Autolus

CLINICAL STUDY PROTOCOL

A SINGLE-ARM, OPEN-LABEL, MULTI-CENTRE, PHASE I/II STUDY EVALUATING THE SAFETY AND CLINICAL ACTIVITY OF AUTO3, A CAR T CELL TREATMENT TARGETING CD19 AND CD22 WITH ANTI PD-1 ANTIBODY IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

Short Study Title:	ALEXANDER
Protocol Number:	AUTO3-DB1
Study Products:	AUTO3 for i.v. infusion; and pembrolizumab
Development Phase:	I/II
Sponsor:	Autolus Limited Forest House 58 Wood Lane White City London, W12 7RZ United Kingdom (UK)
Protocol Version:	Version 10.0
EudraCT Number:	2016-004682-11
Protocol Date:	06 May 2021
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

ADMINISTRATIVE AND CONTACT INFORMATION

Sponsor:

United Kingdom	**European Union Legal Representative**	**United States of America**
Autolus Limited	Autolus GmbH	Autolus Inc
Forest House 58 Wood Lane White City London, W12 7RZ	Arnulfpark Luise-Ullrich-Straße 20 D-80636 Munich Germany	805 King Farm Blvd. Suite 550 Rockville, MD 20850

Contact List

The List of Service Providers for the study will be maintained separately by Autolus Limited and kept in the Trial Master File.

Chief Investigator:

Primary Medical Monitor

Secondary Medical Monitor:

Notification of SAEs:

24-hour SAE Hotline:

SPONSOR SIGNATURE PAGE

Study Title: A Single-arm, Open-label, Multi-centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD-1 Antibody in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma.

Short Study Title:	ALEXANDER
Protocol Number:	AUTO3-DB1
Version Number:	10.0
Version Date:	06 May 2021

I have read the protocol AUTO3-DB1 titled "A Single-arm, Open-label, Multi-centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD-1 Antibody in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

This document has been electronically signed within the electronic data management system. Please refer to the last page of the document for the electronic signature.

Signature	Date (DD MMM YYYY)
[redacted]	

INVESTIGATOR SIGNATURE PAGE

Study Title: A Single-arm, Open-label, Multi-centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD-1 Antibody in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma.

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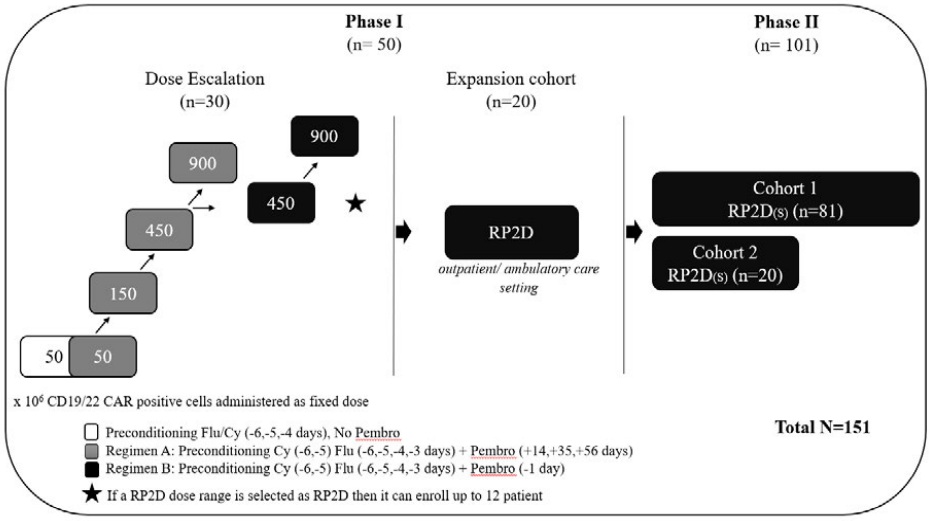
Changes to the protocol will only be implemented after written approval is received from Autolus Limited and the Institutional Review Board or Independent Ethics Committee (as appropriate), with the exception of medical emergencies. I will ensure that study staff fully understand and follow the protocol.

Signature	Date
Name and address:	(DD MMM YYYY)

PROTOCOL SYNOPSIS

Title	A Single-arm, Open-label, Multi-centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD-1 Antibody in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma.
Short Title	ALEXANDER
Protocol Number	AUTO3-DB1
Sponsor	Autolus Limited
Phase	I/II
Study Product	AUTO3, an advanced therapy investigational medicinal product (ATIMP), consisting of autologous enriched T cells retrovirally transduced to express two Chimeric Antigen Receptors (CARs), targeting cluster of differentiation (CD) 19 and/or CD22.
Study Population	Patients with confirmed diagnosis of diffuse large B cell lymphoma (DLBCL) and large B cell lymphoma subsets who have relapsed or refractory disease.
Study Duration	The study will take approximately 7 years from first patient enrolled until the end of the study. The end of the study is defined as the last patient last visit (LPLV) expected to be 36 months after the last patient has received AUTO3 infusion or earlier, in the event of patient death or consent withdrawal.
Overview	A single-arm, open-label, multi-centre, Phase I/II dose escalation and expansion study to determine the safety and clinical activity of AUTO3 administered intravenously (i.v.) with consolidation or pre-conditioning with anti-programmed cell death protein 1 (PD-1) antibody (pembrolizumab) in patients with relapsed or refractory DLBCL and large B cell lymphoma subsets. AUTO3 is an ATIMP consisting of autologous enriched T cells retrovirally transduced to express two CARs, targeting CD19 and/or CD22 on the same cell. AUTO3 cells express second generation CARs in which the CD19 CAR construct uses OX40-ζ endodomains and the CD22 CAR uses 41BB-ζ endodomains. AUTO3 will be administered following lymphodepletion with fludarabine (FLU) and cyclophosphamide (CY). In addition, a limited duration of consolidation or pre-conditioning therapy with anti-PD-1 antibody (pembrolizumab) will be administered. This first in human study will assess the safety of AUTO3, determine the appropriate dose and dosing schedule for Phase II of the study, and evaluate the preliminary efficacy of the AUTO3 in patients with relapsed or refractory DLBCL and large B cell lymphoma subsets.

<table>
<tr><td>Primary Objective(s) and Endpoints</td><td>The primary objectives and endpoints of the study are as follows:
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Phase I</td></tr>
<tr><td colspan="2">Escalation</td></tr>
<tr><td>To assess the safety and tolerability of AUTO3 administration with pembrolizumab.</td><td>Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.</td></tr>
<tr><td>To identify the recommended Phase II dose(s) and maximum tolerated dose (MTD), if an MTD exists, of AUTO3.</td><td>Frequency of dose limiting toxicity of AUTO3.</td></tr>
<tr><td colspan="2">Expansion</td></tr>
<tr><td>To assess the safety and tolerability of AUTO3 administration with pembrolizumab in the outpatient/ambulatory care setting</td><td>Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.</td></tr>
<tr><td colspan="2">Phase II</td></tr>
<tr><td>To evaluate the clinical efficacy of AUTO3 at the recommended Phase II dose(s) with pembrolizumab for Cohort 1.
To assess the overall safety and tolerability of AUTO3 with pembrolizumab in Cohort 2 at the recommended Phase II dose(s).</td><td>Best overall response post-AUTO3 infusion.
Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.</td></tr>
</table></td></tr>
<tr><td>Study Design</td><td>This is a Phase I/II, open-label, multi-centre study to characterise the safety and clinical activity of AUTO3 with anti-PD-1 antibody (pembrolizumab) when administered to patients with relapsed or refractory DLBCL and its defined subsets. The study will consist of two parts, a Phase I, dose escalation and expansion, followed by a Phase II. Both parts of the study will involve patients going through the following six sequential stages: screening, leukapheresis, pre-conditioning, treatment, consolidation, and follow-up-.
Phase I:
Dose escalation: To identify the optimal dose (based on safety, tolerability, and anti-tumour activity) of AUTO3 using a rolling 6 dose escalation design. Up to four dose levels and approximately 30 patients with DLBCL (and its defined subsets) will be treated. Doses from 50×10^6 to 900×10^6 CD19/CD22 CAR -positive T cells administered as a single dose will be evaluated. All patients (except the first three patients in the dose level 1 cohort) will receive limited consolidation or pre-conditioning therapy with pembrolizumab.
Expansion cohort: To assess the safety and tolerability of AUTO3 at the recommended phase 2 dose(s) (RP2Ds) or dose range and pembrolizumab regimen identified in the dose escalation part. Approximately 20 patients with DLBCL will be treated in an outpatient/ambulatory care setting.
Phase II: To further characterise the safety and assess the efficacy of AUTO3 at the recommended dose(s) or dose range identified in Phase I, approximately up to 101 patients will be treated in Phase II (81 patients with DLBCL subsets and transformed follicular lymphoma in Cohort 1 and, additionally, 20 patients in Cohort 2 with primary mediastinal large B cell lymphoma and those with lymphoma transformed from other indolent histologies).
Biomarkers relating to the CAR T cells, B cells, and tumour cells will be evaluated in all patients. All patients treated in Phase I and II of the study will</td></tr>
</table>

	attend clinic visits for up to 36 months post-AUTO3 infusion (or less in case of withdrawal) for study-specific assessments including adverse event (AE) assessments, physical examination, and clinical laboratory and immunology tests. At the end of the study, or following early withdrawal from this study, all patients will be invited to enrol on a long-term follow-up study protocol (AUTO-LT1) and followed until death or withdrawal of consent for up to 15 years following last treatment with AUTO3. 
Number of Patients	Approximately to 171 patients in total are expected to be enrolled (consented) into Phase I and Phase II of the study and approximately 151 patients in total are anticipated to be treated with AUTO3 therapy. • **Phase I:** approximately 50 treated patients in total. Including 3 to 6 patients per dose cohort following a rolling 6 dose escalation design, and approximately 12 patients at the RP2D/dose range, and 20 patients in the expansion cohort. • **Phase II:** up to 81 evaluable patients, using Simon's 2-stage optimal design in Cohort 1; an additional 20 patients in Cohort 2 (a total of 101 patients).
Key Criteria for Eligibility	Only patients whose leukapheresate sample has been successful in generating AUTO3 in adequate quantity and quality will be treated. The criteria for patient eligibility are summarised as follows: **Inclusion Criteria:** Patients must meet all the following criteria for study entry: 1. Male or female, aged ≥18 years. 2. Willing and able to give written, informed consent to the current study. 3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1. 4. Histologically confirmed DLBCL and large B cell lymphoma) subsets, including: **Phase I and Phase II Cohort 1:**

a) DLBCL, not otherwise specified (NOS), per World Health Organisation classification and DLBCL with MYC and BCL2 and/or BCL6 rearrangements (double/triple hit).

b) Transformed DLBCL from follicular lymphoma.

c) High-grade B cell lymphoma with MYC expression (excluding Burkitt's lymphoma).

Phase I and Phase II Cohort 2:

d) Transformed DLBCL from other indolent lymphomas (excluding Richter's transformation).

Primary mediastinal large B cell lymphoma.

5. Chemotherapy-refractory disease, defined as one or more of the following:
   a) Stable disease (duration of stable disease must be ≤12 months) or progressive disease as best response to most recent chemotherapy containing regimen. Refractory disease after frontline chemo-immunotherapy is allowed.
   b) Disease progression or recurrence in ≤12 months of prior autologous haematopoietic stem cell transplantation (ASCT).

OR

6. Relapse after at least two lines of therapy or after ASCT. At a minimum:
   a) Patients must have received rituximab or another anti-CD20 monoclonal antibody (unless Investigator determines that tumour is CD20-negative) and an anthracycline-containing chemotherapy regimen.
   b) Patients must have either failed ASCT, or be ineligible for or not consenting to ASCT.
   c) Patients with transformed DLBCL must have received at least one line of therapy after transformation to DLBCL.
7. Positron emission tomography (PET)-positive disease per Lugano classification.
8. For females of childbearing potential (defined as <24 months after last menstruation or not surgically sterile), a negative serum or urine pregnancy test must be documented at screening, prior to pre-conditioning and confirmed before receiving the first dose of study treatment.

   For females who are not postmenopausal (<24 months of amenorrhea) or who are not surgically sterile (absence of ovaries and/or uterus), two methods of contraception comprising one highly effective method of contraception together with a barrier method must be used during the treatment period and for at least 12 months after the last dose of study treatment. They must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 12 months after receiving the last dose of study drug (please refer to Appendix 3).
9. For males, it must be agreed that two acceptable methods of contraception are used (one by the patient – usually a barrier method, and one highly effective method by the patient's partner as defined in Appendix 3) during the treatment period and for at least 12 months after the last dose of study treatment and that sperm will not be donated

during the treatment period and for at least 12 months after the last dose of study treatment.

10. Adequate renal, hepatic, pulmonary, and cardiac function defined as:
    a) Creatinine clearance ≥40 cc/min.
    b) Serum alanine aminotransferase/aspartate aminotransferase ≤2.5 × upper limit of normal (ULN).
    c) Total bilirubin ≤1.5 × ULN, except in patients with Gilbert's syndrome.
    d) Left ventricular ejection fraction (LVEF) ≥50% (by echocardiogram [ECHO] or multigated acquisition [MUGA]) unless the institutional lower limit of normal is lower.
    e) Baseline oxygen saturation >92% on room air and ≤Grade 1 dyspnoea.
11. Patient has adequate bone marrow function without requiring ongoing blood product or granulocyte-colony stimulating factor support and meets the following criteria:
    a) Absolute neutrophil count ≥1.0 × 10^9/L.
    b) Absolute lymphocyte count ≥0.3 × 10^9/L (at enrolment and prior to leukapheresis).
    c) Haemoglobin ≥80 g/L.
    d) Platelets ≥75 × 10^9/L.
12. No contra-indications for leukapheresis.

Exclusion Criteria:

Patients meeting any of the following exclusion criteria must not be enrolled into the study:

1. Prior allogeneic haematopoietic stem cell transplant.
2. Females who are pregnant or lactating.
3. History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, paresis, aphasia, stroke within 3 months prior to enrolment, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, uncontrolled mental illness, or psychosis.
4. Patients with active CNS involvement by malignancy. Patients with history of CNS involvement with malignancy may be eligible if CNS disease has been effectively treated and provided treatment was at least 4 weeks prior to enrolment (at least 8 weeks prior to AUTO3 infusion).
5. Clinically significant, uncontrolled heart disease (New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, sick-sinus syndrome, or electrocardiographic evidence of acute ischaemia or Grade 3 conduction system abnormalities unless the patient has a pacemaker) or a recent (within 12 months) cardiac event.
    - Uncontrolled cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded).
    - Evidence of pericardial effusion.
6. Patients with a history (within 3 months) or evidence of pulmonary embolism requiring ongoing therapeutic anticoagulation at the time of pre-conditioning.

	7. Patients with active gastrointestinal (GI) bleeding. 8. Patients with any major surgical intervention in the last 3 months. 9. Active bacterial, viral or fungal infection requiring systemic treatment. Active or latent hepatitis B infection or hepatitis C infection. Testing positive for human immunodeficiency virus, human T cell lymphotropic virus (HTLV1 and 2) or syphilis. 10. History of autoimmune disease (e.g. Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 24 months. 11. Patients with a known history or prior diagnosis of optic neuritis or other immunologic or inflammatory disease affecting the CNS. 12. Evidence of active pneumonitis on chest computed tomography (CT) scan at screening or history of drug-induced pneumonitis, idiopathic pulmonary fibrosis, organising pneumonia (e.g. bronchiolitis obliterans), or idiopathic pneumonitis. Prior radiation pneumonitis in the radiation field (fibrosis) is allowed (if >24 weeks since the event). 13. History of other malignant neoplasms unless disease free for at least 24 months (carcinoma *in situ*, non-melanoma skin cancer, breast or prostate cancer on hormonal therapy allowed). 14. Prior treatment with PD-1, Programmed cell death ligand 1 (PD-L1), or cytotoxic T lymphocyte-associated protein 4 targeted therapy, or tumour necrosis factor (TNF) receptor superfamily agonists including CD134 (OX40), CD27, CD137 (41BB), and CD357 (glucocorticoid-induced TNF receptor family-related protein) within 6 weeks prior to AUTO3 infusion (excluding study treatment with pembrolizumab on Day -1). 15. Prior treatment with investigational or approved gene therapy or cell therapy products until a dose level has treated at least three patients and has been declared safe. 16. Prior CD19 or CD22 targeted therapy. 17. The following medications are excluded: • Steroids: Therapeutic doses of corticosteroids within 7 days of leukapheresis or 72 hours prior to AUTO3 administration. However, physiological replacement, topical, and inhaled steroids are permitted. • Immunosuppression: Immunosuppressive medication must be stopped ≥2 weeks prior to leukapheresis or AUTO3 infusion. • Cytotoxic chemotherapies within 2 weeks of AUTO3 infusion and 1 week prior to leukapheresis (2 weeks for lymphodepleting chemotherapy). • Antibody therapy use including anti-CD20 therapy within 2 weeks prior to AUTO3 infusion, or 5 half-lives of the respective antibody, whichever is shorter. • Granulocyte-colony stimulating factor less than 10 days prior to leukapheresis. • Live vaccine ≤4 weeks prior to enrolment.

	• Prophylactic intrathecal therapy: Methotrexate within 4 weeks and other intrathecal chemotherapy (e.g. Ara-C) within 2 weeks prior to starting pre-conditioning chemotherapy. 18. Prior limited radiation therapy (e.g. radiation to bone metastasis for pain control) within 4 weeks of AUTO3 infusion or chest/mediastinal radiation within 24 weeks of AUTO3 infusion. 19. Research participants receiving any other investigational agents, or concurrent biological, chemotherapy, or radiation therapy. 20. Known allergy to albumin, dimethyl sulphoxide, CY or FLU, pembrolizumab or tocilizumab. 21. Any contraindications to receive anti-PD-1 antibody pembrolizumab will be excluded from cohorts requiring administration of pembrolizumab. 22. Patients, who in the opinion of the Investigator, may not be able to understand or comply with the safety monitoring requirements of the study. 23. Any other condition that in the Investigator's opinion would make the patient unsuitable for the clinical trial. **Phase I expansion cohort:** 24. Subjects who do not have caregiver support (in line with institutional outpatient transplant guidelines) for outpatient/ambulatory care setting. 25. Subjects who are staying greater than 60 minutes (or whatever is permissible per institutional outpatient transplant guidelines) from the clinical trial site at the time of treatment. PATIENT ELIGIBILITY TO RECEIVE AUTO3: Patients meeting any of the following criteria must not initiate pre-conditioning or infusion with AUTO3 (or pembrolizumab on Day 1) or- must have the AUTO3 infusion delayed until they no longer meet these criteria: 1. Severe intercurrent infection. 2. Requirement for supplementary oxygen or active pulmonary infiltrates. 3. Clinical deterioration of organ function (renal and hepatic) exceeding the criteria set at study entry.
Study Product Dose, Dosing Regimen, and Administration	Eligible patients will receive a single dose i.v. infusion of AUTO3 following pre-conditioning treatment. The AUTO3 product contains both transduced (CD19/CD22 CAR-positive) and non-transduced T cells. The dose is expressed as the number of CD19/CD22 CAR-positive T cells. Starting dose will be 50×10^6 CD19/CD22 CAR-positive T cells administered as a single dose. The highest planned dose to be evaluated is 900×10^6 CD19/CD22 CAR-positive T cells. All patients will be monitored for up to 10 days following AUTO3 administration (inpatient or ambulatory care setting).
Pre-conditioning Treatment and Consolidation	All patients will receive a pre-conditioning regimen using i.v. FLU followed by i.v. CY. FLU 30 mg/m^2 will be given on Days -6, -5, -4, and -3 and CY 500 mg/m^2 will be given on Days -6 and -5. Regimen A will comprise 3 doses of pembrolizumab (200 mg i.v. on Days 14, 35, and 56) as consolidation.

	Regimen B will comprise 1 dose of pembrolizumab (200 mg i.v. on Day -1) during pre-conditioning.
Safety Evaluation	Safety will be assessed by physical examination, vital signs, clinical laboratory tests, electrocardiograms, AE and severe AE monitoring, performance status assessments and concomitant medication usage. The severity of AEs will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 5.0). Cytokine Release Syndrome (CRS) and neurological toxicity will be graded according to the American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation (ASTCT/ASBMT) consensus grading (Lee et al. 2019).
Efficacy Evaluation	Efficacy will be evaluated as per Lugano Classification. Response evaluations will be assessed by PET scans, CT scans, magnetic resonance imaging (MRI) and physical examination. Efficacy assessments for Phase II will be performed by the Investigators and independent central radiology review.
Biomarker Evaluation	Biomarker evaluation will include the following: • Expansion and persistence of CD19/CD22 CAR-positive T cells as determined by polymerase chain reaction and/or flow cytometry. • Depletion of CD19 and/or CD22 cell compartment as determined by flow cytometry and/or immunohistochemistry on bone marrow.
Special Study Procedures	All patients will undergo an unstimulated leukapheresis for AUTO3 generation.
Statistical Analysis	Continuous data will be summarised using the mean, median, standard deviation, minimum and maximum, while frequency counts and percentages will be presented for discrete variables. Time-to-event endpoints will be summarised using the Kaplan-Meier method. Where appropriate, a 2-sided 95% confidence interval will be presented with the estimates. Data from all treated patients (Safety set) will be used for safety analyses and will be summarised by dose level. Efficacy analysis set (EAS) and other analysis sets will be defined for the efficacy analyses.
Interim Analysis	An end of Phase I analysis will be performed. The overall response rate will be calculated. If the upper limit of the 95% confidence interval is less than 30% for patients treated at the RP2D(s), the study will be stopped. If the upper limit of the 95% confidence interval is over 30%, the study will continue to the Phase II part of the study. In Phase II of the study, an interim analysis on response rates will be performed after 27 patients are treated in Cohort 1 and considered evaluable (12 weeks post-treatment of 27th evaluable patient). The study will be stopped in this first stage if no more than nine responses have been observed. If the response rate has exceeded interim analysis stopping criteria prior to 27 evaluable patients having been treated, then the study will continue to full recruitment without stopping. A formal interim analysis will still be performed based on the first 27 evaluable patients.

SCHEDULE OF ASSESSMENTS:

Table 1: Assessments from Screening to End of Treatment Phase

Visits / Assessments	Screening		Leuka-pheresis	FLU-CY Pre-Conditioning	AUTO3 Treatment and Monitoring				
	Day -84 to -35*	Day -35 to -6	Day -84 to -35*	Day -6, -5, -4, -3, -1 (-1d)	Day -1 (+1 d)	Day 0	Days 1 to 18 (±2d) (10-day monitoring#)	Day 20 (+3d)	**Day 28 (±3d)
Informed consent	X								
Enrolment confirmation[1]			X						
Demographic data[2]	X								
Eligibility criteria [3]	X			X^{D-6}		X			
Medical/lymphoma history [4]	X			X^{D-6}					
Lymphoma B-symptoms assessment	X					X			X
Survival Status[5]	$X^{[25]}$								
EXAMINATIONS/INVESTIGATIONS									
ECOG performance status	X			X^{D-6}					X
Physical examination [6]	X			X^{D-6}		X	$X^{D1, D7, D14}$	X	X
Weight	X		X	X^{D-6}					X

Visits / Assessments	Screening		Leuka-pheresis	FLU-CY Pre-Conditioning	AUTO3 Treatment and Monitoring				
	Day -84 to -35*	Day -35 to -6	Day -84 to -35*	Day -6, -5, -4, -3, -1 (-1d)	Day -1 (+1 d)	Day 0	Days 1 to 18 (±2d) (10-day monitoring[#])	Day 20 (+3d)	**Day 28 (±3d)
Vital signs and oxygen saturation [7]	X			X^{D-6}		X	$X^{D1, D7, D14}$	X	X
12-lead ECG [8]	X			X^{D-6}					
ECHO or MUGA [9]	X								
DISEASE ASSESSMENT AND MONITORING									
Tumour sample [10]		X					X^{D14}		
CT or MRI imaging (neck, chest, abdomen, and pelvis)		X							X
[^{18}F]-FDG PET scan (skull base to the proximal femur) [11]		X							X
Bone marrow aspirate ± trephine (6 mL in ACD-A tubes) [12]		X							
SAFETY EVALUATIONS									
Haematology [13]	X		X	X^{D-6}	X		$X^{D1, D7, D14}$	X	X
Biochemistry [14]	X		X	X^{D-6}	X		$X^{D1, D7, D14}$	X	X
Ferritin, C reactive protein				X^{D-6}	X		$X^{D1, D4, D7, D10, D12, D14, D16, D18}$	X	X
Coagulation [15]			X		X		$X^{D1, D7, D14}$	X	X

Visits / Assessments	Screening		Leuka-pheresis	FLU-CY Pre-Conditioning	AUTO3 Treatment and Monitoring				
	Day -84 to -35*	Day -35 to -6	Day -84 to -35*	Day -6, -5, -4, -3, -1 (-1d)	Day -1 (+1 d)	Day 0	Days 1 to 18 (±2d) (10-day monitoring#)	Day 20 (+3d)	**Day 28 (±3d)
IgG, IgM, IgA				X^{D-6}					X
Infectious disease screen [16]	X		X						
Flow cytometry for B cells				X^{D-6}					X
Pregnancy test [17]	X	X		X^{D-6}	X				X
PHARMACOKINETICS, PHARMACODYNAMICS AND BIOMARKER ASSAYS									
Blood for cytokines[18]		X		X^{D-6}	X		$X^{D1, D4, D7, D10, D12, D14, D16, D18}$	X	X
AUTO3 persistence[19]					X		$X^{D1, D4, D7, D10, D12, D14, D16, D18}$	X	X
RCR[20]		X							X
Blood for immunological/ genomic profiling of CAR T cells [21]							$X^{D7, D14}$	X	X
TREATMENTS									
FLU-CY				$X^{D-6, D-5, D-4, D-3}$					
AUTO3 infusion						X			
Regimen A: Pembrolizumab × 3 doses[22]							X^{D14}		

Visits / Assessments	Screening		Leuka-pheresis	FLU-CY Pre-Conditioning	AUTO3 Treatment and Monitoring				
	Day -84 to -35*	Day -35 to -6	Day -84 to -35*	Day -6, -5, -4, -3, -1 (-1d)	Day -1 (+1 d)	Day 0	Days 1 to 18 (±2d) (10-day monitoring[#])	Day 20 (+3d)	**Day 28 (±3d)
Regimen B: Pembrolizumab × 1 dose[23]				X^{D-1}					
ADVERSE EVENTS									
Adverse event [24]	X								
Concomitant medication [25]				Following start of pre-conditioning until Day 75 post-AUTO3 infusion					

Abbreviations: β-Hcg= β-human chorionic gonadotropin; ACD-A=anticoagulant citrate dextrose solution A; AE=adverse event; AESI=adverse event of special interest; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSA=body surface area; CAR=chimeric antigen receptor; CD=cluster of differentiation; CMR=complete metabolic response; CPK=creatine phosphokinase; CR=complete response; CT=computed tomography; CY=cyclophosphamide; d=day; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ECHO=echocardiogram; eCRF=electronic case report form; FDG=fluorodeoxyglucose; FLU=fludarabine; HTLV-1/-2=human T cell lymphotropic virus-1/-2; Ig=immunoglobulin; ICANS=immune effector cell-associated neurotoxicity syndrome; max=maximum; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; PD-1=programmed cell death protein 1; PET=positron emission tomography; RCR=replication competent retrovirus, Reg=regimen; SAE=serious adverse event

#: Monitoring is defined as in-hospital stay or ambulatory care admission with at least once a day evaluation by a physician or qualified designee. During the Phase I expansion cohort, monitoring at a minimum every 2 to 3 days for 10 days (in the UK, evaluation at least once a day for 10 days by a physician or qualified designee).

*: Treatment initiation may occur earlier than 35 days depending on time of completion of manufacture and satisfactory screening.

**: End of dose limiting toxicity period set as follows: 28 days after dose of AUTO3 (or 2 weeks after the first dose of pembrolizumab if administration is delayed past Day 14). Patients eligible for re-treatment will undergo assessments from Day -6 onwards unless repeat leukapheresis is required, in which case assessments will be performed from the leukapheresis visit onwards, as per schedule of assessments.

$X^{D3, D7 etc}$ Test to be performed on a particular day of the schedule rather than systematically at every visit. Please refer to the number to determine the day of assessment.

$X^{\dagger}$ Sample to be taken if analysis of previous sample showed detectable CAR T cells.

1. Enrolment confirmed once all inclusion/exclusion criteria have been fulfilled and leukapheresis has been accepted for manufacturing.
2. Demographic data: Race/ethnicity, height, age, and gender.
3. Eligibility criteria: To be re-assessed prior to pre-conditioning and AUTO3 infusion.
4. Medical/lymphoma history: To include clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), known allergies and prior medications. Record disease status at last assessment and complications since last assessments.
5. Survival Status: all enrolled patients will be followed up for survival. If a visit is skipped where survival status is required or if the timepoint does not align with a scheduled visit, the information can be obtained over the phone.

6. Physical examination: Complete physical examination to be performed at screening including a complete neurological examination then focused examination as appropriate at following visits.
7. Vital signs: Temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturations will be performed. On Day 0 of any treatment phase, record vital signs immediately prior to AUTO3 infusion and every 30 minutes (±10 minutes) for 4 hours post-AUTO3 infusion, and thereafter monitored as per hospital policy but no less than once a day during hospital/ambulatory stay. During the Phase I expansion cohort, monitoring at a minimum every 2 to 3 days for 10 days. If clinically significant report as an AE as appropriate. Body surface area (BSA) to be recorded on Day -6.
8. ECG: May be repeated when clinically indicated such as severe CRS.
9. ECHO (preferred method) or MUGA: To be performed at screening and to be repeated if patient experiences CRS or if clinically indicated. Same method should be used throughout the study.
10. Fresh (or archived) tumour tissue sample should be obtained where possible at screening (or at the most recent relapse), Day 14 (±7 days) and at disease progression.
11. For those patients receiving a bridging chemotherapy regimen, the baseline PET/CT scans must be done after completion of bridging therapy and before pre-conditioning and AUTO3 infusion. [^{18}F]-FDG PET scan: If at 6 months the patient has a CMR on PET scan, CT scans alone may be used for future assessment time points, if clinically appropriate. If relapse occurs after CMR or disease progression is suspected (e.g. new or enlarging lesion(s) detected on CT scan), a PET scan is to be repeated to confirm relapse/progression.
12. Bone marrow aspirate and biopsy: 6 mL (2 mL+ 4 mL) Bone marrow aspirate in ACD-A for evaluation of disease in marrow, biopsy is optional. Repeat aspirate/biopsy is required to confirm complete response if bone marrow involvement at baseline. Sample may also be used for biomarker evaluation. Samples will be sent to a central laboratory for analysis as detailed in the laboratory manual.
13. Haematology: Full blood count: haemoglobin, red blood cell count, platelet count, white blood cell count with differential. During hospitalisation when this is performed daily as standard care, only results from the indicated time points will be recorded in the eCRF. Additional time points will be recorded if clinically appropriate or associated with AEs. Full blood count to be performed prior to chemotherapy on first day of pre-conditioning days and prior to AUTO3 infusion on Day 0 (or pembrolizumab on Day-1, whichever is first) of any treatment phase.
14. Biochemistry: Sodium, phosphate, potassium, ALT, AST, urea, uric acid, creatinine, CPK, lactate dehydrogenase, total bilirubin, calcium, albumin, and results from the indicated time points will be recorded in the eCRF. Additional time points will be recorded if clinically appropriate or associated with AEs. All tests must be performed prior to AUTO3 infusion on Day 0. Glomerular filtration rate should be calculated at screening as per institutional preferred method. After Month 3 only clinically relevant assays will be performed.
15. Coagulation: Prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen.
16. Infectious disease screen: Human immunodeficiency virus, hepatitis B, hepatitis C, human T-lymphotropic virus-1, human T-lymphotropic virus-2, syphilis, (max 30 days before leukapheresis). Results must be available prior to leukapheresis. If required, an additional sample will be taken on the day of leukapheresis (or within 7 days of leukapheresis).
17. Pregnancy test: Serum (β-Hcg) or urine pregnancy testing for women of childbearing potential.
18. Blood for cytokines: Serum cytokine sample to be taken prior to pre-conditioning on Day -6. To be collected daily during cytokine release syndrome until it resolves or clinically indicated. During hospital stay, sample collection to be performed as per schedule of assessments (±2 days). Refer to laboratory manual for collection instructions. Additional optional samples may be collected between Day -3 and Day 0 if patient is hospitalised or in outpatient/ambulatory care. Based on emerging data, additional optional blood samples may be collected to assess the drug levels of FLU-CY prior to pre conditioning on Day-6 and approximately 1 hour or later after pre-conditioning on Day -6 and Day -3.
19. AUTO3 persistence: 9 mL Lithium Heparin tube and 2.5 mL DNA PAXgene tube should be collected on visits as indicated, sent to central analysis as described in the lab manual. Additional samples may be collected if clinically appropriate. An optional sample will be collected at time of disease progression. Sample collection may be modified based on patient body weight.
20. RCR: 5 mL blood in Lithium Heparin tubes will be taken on visits as indicated for cryopreservation of peripheral blood mononuclear cells and plasma in case RCR or integration site analysis is required and to central analysis as described in the lab manual.
21. Blood for immunological and genomic profiling of CAR T cells: Blood collected in 2 × 10 mL Lithium Heparin tubes to be taken on visits as indicated for cryopreservation of peripheral blood mononuclear cells and plasma for immunological and genomic profiling of CAR T cells and other assays as developed. Samples may be collected at additional time points based on emerging data.
22. Anti-PD-1 antibody (pembrolizumab) will be administered (according to the pembrolizumab dosing schedule the patient is assigned to) on Regimen A Day 14 (±3 days) and then every 3 weeks for a total of 3 doses. However, administration may be delayed until any ongoing CRS or neurotoxicity has resolved in Regimen A. Patients will be monitored (inpatient or outpatient/ambulatory care setting) for 3 days following the first dose of Regimen A pembrolizumab on Day 14.
23. Anti-PD-1 antibody (pembrolizumab) will be administered on Day -1 as part of the pre-conditioning treatment with FLU-CY (Regimen B)

24. Adverse events will be collected on an ongoing basis throughout the study. After Month 6, all SAEs, all AESI and ONLY non-serious AEs that are deemed related to AUTO3 treatment or study related procedure will be collected. Please refer to Section 12 of the protocol for reporting requirements
25. Prior to Day -6 and after Month 6 only concomitant medications relevant to AUTO3 treatment or study related procedures will be collected.

Note: The total estimated volume of blood collected for safety, biomarkers and immunological assessments (with the exception of the leukapheresis procedure) across any one year will not normally exceed 770 mL. The maximum volume of blood collected on any one day is unlikely to exceed 76 mL. No more than 440 mL of blood will be collected in any 28-day period.

Note: If an assessment was performed as part of the patient's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed informed consent has been obtained provided that the assessments fulfil the study requirements and are performed within the specified timeframe prior to the AUTO3 administration.

Note: Assessments (laboratory or radiological) at additional time points may be performed based on emerging data to better understand the safety/efficacy of the CAR product.

Table 2: Efficacy and Safety Follow-up

Visits / Assessments	EFFICACY & SAFETY FOLLOW-UP									END OF STUDY***
	M2 ±7d	**M3 ±7d**	**M4 ±7d**	**M6 ±7d**	**M9 ±7d**	**M12 ±7d**	**M18 ±7d**	**M24 ±7d**	**q6 Months until EoS ±4 weeks**	**EoS / Early Withdrawal**
PATIENT INFORMATION										
Concomitant Medication [1]	X									
Survival Status [2]	X									
EXAMINATIONS, INVESTIGATIONS & SAFETY EVALUATIONS										
Performance status [3]		X		X		X	X^{q1y}			
Weight		X		X		X	X^{q1y}			
Physical examination [4]	X	X	X	X	X	X	X^{q1y}			X
Vital signs [5]	X	X	X	X	X	X	X^{q1y}			X
IgG, IgM, IgA levels		X		X		X	X^{q1y}			
Haematology [6]	X	X	X	X	X	X	X as clinically indicated			X
Biochemistry [7]	X	X	X as clinically indicated							X

Visits / Assessments	EFFICACY & SAFETY FOLLOW-UP									END OF STUDY***
	M2 ±7d	**M3 ±7d**	**M4 ±7d**	**M6 ±7d**	**M9 ±7d**	**M12 ±7d**	**M18 ±7d**	**M24 ±7d**	**q6 Months until EoS ±4 weeks**	**EoS / Early Withdrawal**
Coagulation [8]	X as clinically indicated e.g. severe CRS									
Pregnancy test [9]	X	X		X		X	X	X		X
Adverse events [10]	X									
DISEASE ASSESSMENTS										
Overall disease assessment [11]		X		X	X	X	X^{q1y}			X
CT or MRI imaging (neck, chest, abdomen, and pelvis) [12]		X		X	X	X	X^{q1y}			
[^{18}F]-FDG PET scan) skull base to the proximal femur) [12]		X		X	X	X	X^{q1y}			
Bone marrow aspirate ± trephine [13]	X to confirm complete response									
BIOMARKERS										
Tumour sample [14]	X at relapse									
Peripheral Blood										

Visits / Assessments	EFFICACY & SAFETY FOLLOW-UP									END OF STUDY***
	M2 ±7d	**M3 ±7d**	**M4 ±7d**	**M6 ±7d**	**M9 ±7d**	**M12 ±7d**	**M18 ±7d**	**M24 ±7d**	**q6 Months until EoS ±4 weeks**	**EoS / Early Withdrawal**
Cytokine Profile		X								
AUTO3 persistence [15]	X	X	X	X	X	X	X	X	X	
Immunogenicity [15]	X									
Immunophenotyping of AUTO3 [15]		X		X		X	X	X		
Genomic profiling [16]		X		X		X		X		
RCR [17]		X		X		X		X	X^{q1y}	X
Insertional Mutagenesis [18]		X		X		X		X	X^{q1y}	X

Abbreviations: β-Hcg= β-human chorionic gonadotropin; ACD-A=anticoagulant citrate dextrose solution A; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CAR=chimeric antigen receptor; CMR=complete metabolic response; CR=complete response; CSF=cerebrospinal fluid; CT=computed tomography; D=day; ECOG=Eastern Cooperative Oncology Group; ECHO=echocardiogram; eCRF=electronic case report form; EoS= End of Study; GFR=glomerular filtration rate; HTLV-1/-2=human T cell lymphotropic virus1/-2; ICANS=immune effector cell-associated neurotoxicity syndrome; Ig=immunoglobulin; i.v.=intravenous; LDH=lactate dehydrogenase; M=month; MRI=magnetic resonance imaging; MUGA= multigated acquisition scan; NGS=next generation sequencing; PCR=polymerase chain reaction; PET=positron emission tomography; q1y=once per year; RCR=replication competent retrovirus.

*** The end of the study (EoS) is defined as the LPLV expected to be 36 months after the last treated patient with AUTO3 or earlier in the event of patient death or consent withdrawal.

1. Prior to Day -6 and after Month 6 only concomitant medications relevant to AUTO3 treatment or study related procedures will be collected.
2. Survival Status: all enrolled patients will be followed up for survival. If a visit is skipped where survival status is required or if the timepoint does not align with a scheduled visit, the information can be obtained over the phone.
3. Performance status: Performance status will be assessed by using ECOG.
4. Physical examination: Complete physical examination to be performed at screening and Day -6 then focused examination as appropriate at following visits.
5. Vital signs: Temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation will be performed. On dosing day, perform vital signs immediately prior to AUTO3 infusion and then hourly (±15 minutes) for 4 hours post infusion, and thereafter monitored no less than 2 to 3 days during hospital/ambulatory stay. Vital signs also to be performed if clinically indicated. Additional values considered as clinically significant abnormalities will be recorded as AEs.
6. Haematology: Haemoglobin, platelet count, and white blood cell count with differential (neutrophils, monocytes and lymphocytes). This is performed daily during admission as standard care and results from the indicated time points will be recorded in the Electronic Case Report Form (eCRF).

7. Biochemistry: AST/ALT, alkaline phosphatase, LDH, total bilirubin, urea/blood urea nitrogen, creatinine, uric acid. GFR should be calculated at screening as per the institutional preferred method. The results from the indicated time points will be recorded in the eCRF. These tests are generally performed daily during admission as part of standard care. All tests must be performed prior to AUTO3 infusion on the dosing day.
8. Coagulation: Prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen after baseline assessment may be repeated if patient experiences severe cytokine release syndrome.
9. Pregnancy test: Serum (β-hCG) or urine pregnancy testing for women of childbearing potential.
10. Adverse events: Adverse events will be collected on an ongoing basis throughout the study. After M6, all SAEs, AESI and ONLY non-serious AEs that are deemed related to AUTO3 treatment or study related procedure will be collected. Please refer to Section 12.3 of the protocol for reporting requirements.
11. Overall disease assessment: Once the patient has completed 24 months during the efficacy and safety follow-up, the overall disease assessment will be done by the Investigator reported outcome.
12. Imaging: For those patients receiving a bridging chemotherapy regimen, the baseline PET/CT scans must be done after completion of bridging therapy and before pre-conditioning and AUTO3 infusion. [18F]-FDG PET scan: If at 6 months the patient has a CMR on PET scan, CT scans alone may be used for future assessment time points, if clinically appropriate. If relapse occurs after CMR or disease progression is suspected (e.g. new or enlarging lesion(s) detected on CT scan), a PET scan is to be repeated to confirm relapse/progression.
13. Bone marrow aspirate: Bone marrow aspirate in ACD-A for evaluation of disease in marrow and biopsy are both optional at the time of screening. If performed at screening and there is no evidence of disease, does not need to be repeated. If not performed at screening, then needs to be done to confirm CR. Does not need to be performed if patients do not achieve CR. Assessment for disease involvement is done locally. Sample with lymphoma involvement may also be used for biomarker evaluation.
14. Tumour sample: Fresh (or archived) tumour tissue sample should be obtained where possible at screening (or at the most recent relapse), Day 15 (±7 days) and at disease progression.
15. Biomarkers: Additional samples will be collected at relapse and may be collected in case of safety events or as clinically indicated. Please refer to the laboratory manual. The collection of AUTO3 persistence samples may stop when 2 consecutive samples are not detectable by PCR. In the event of neurotoxicity and CSF is obtained, CSF sample may also be used for AUTO3 persistence. Immunogenicity - assessment of anti-CAR antibodies or anti-CAR T-cell response from blood/serum samples will be done if clinically indicated.
16. Genomic profiling: The collection of samples and the analysis performed are described in Section 9.3.3 of the protocol
17. RCR Testing: If all results are negative during the first-year post first AUTO3 infusion, the subsequent samples will be collected and stored in case further follow-up analysis may be required. After 24 months, the sample for RCR testing will be collected annually until the end of the study.
18. Insertional Mutagenesis: Samples will be collected and stored for subsequent analysis as required.

Note: If an assessment was performed as part of the patient's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed informed consent has been obtained provided that the assessments fulfil the study requirements and are performed within the specified timeframe prior to the AUTO3 infusion.

Table 3: Safety and Survival Follow-up

Visits / Assessments	SAFETY AND SURVIVAL FOLLOW-UP						
	M2[##] ±7d	**M3 ±7d**	**M6 ±7d**	**M12 ±7d**	**M24 ±7d**	**q6 Months until EoS ±4 weeks**	**EoS** / Early Withdrawal**
PATIENT INFORMATION							
Subsequent therapy & response	X						
Survival Status [1]	X						
Concomitant Medication [2]	X						
EXAMINATIONS, INVESTIGATIONS & SAFETY EVALUATIONS							
Pregnancy test		X	X		X		X
Adverse events [3]	X						
Physical Exam	X [q1y]						
BIOMARKERS							
PERIPHERAL BLOOD							
AUTO3 persistence [4]	X [as clinically indicated]						
RCR [5]		X	X	X	X	X[q1y]	X
Insertional Mutagenesis [6]		X	X	X	X	X[q1y]	X

AE=adverse event; AESI=adverse event of special interest; CAR=chimeric antigen receptor; CSF=cerebrospinal fluid; d=day; EoS=end of study; M=Month; PCR=polymerase chain reaction; q6 Months= every six months; RCR=replication competent retrovirus; SAE=serious adverse event. ; q1y=once per year

1. Survival Status: all enrolled patients will be followed up for survival. If a visit is skipped where survival status is required or if the timepoint does not align with a scheduled visit, the information can be obtained over the phone.
2. Prior to Day -6 and after Month 6 only concomitant medications relevant to AUTO3 treatment or study related procedures will be collected.
3. Adverse events: Adverse events will be collected on an ongoing basis throughout the study. After M6, all SAEs, AESI and ONLY non-serious AEs that are deemed related to AUTO3 treatment or study related procedure will be collected. Please refer to Section 12.3 of the protocol for reporting requirements.

4. Biomarkers: Additional samples will be collected at relapse and may be collected in case of safety events or as clinically indicated. Please refer to the laboratory manual. The collection of AUTO3 persistence samples may stop when 2 consecutive samples are not detectable by PCR. In the event of neurotoxicity and CSF is obtained, CSF sample may also be used for AUTO3 persistence. Assessment of Anti-CAR antibodies or anti-CAR T-cell response from blood/serum samples.
5. RCR Testing: If all results are negative during the first-year post first AUTO3 infusion, the subsequent samples will be collected and stored in case further follow-up analysis may be required. After 24 months, the sample for RCR testing will be collected annually until the end of the study.
6. Insertional Mutagenesis: Samples will be collected and stored for subsequent analysis as required.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALL	Acute lymphoblastic leukaemia
ASCT	Autologous haematopoietic stem cell transplantation
ASH	American Society of Hematology
ASTCT/ASBMT	American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation
ATIMP	Advanced therapy investigational medicinal product
AUC	Area under the curve
BM	Bone marrow
BOR	Best overall response
CAR	Chimeric antigen receptor
CD3, -19, -20, -28, -134	Cluster of differentiation 3, 19, 20, 28, 134
CDISC	Clinical Data Interchange Standards
CI	Confidence interval
CMR	Complete metabolic response
CNS	Central nervous system
CR	Complete response, complete remission
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL019	CD19 CAR with 41BB-ζ endodomain
CY	Cyclophosphamide
DFS	Disease-free survival
DLBCL	Diffuse large B cell lymphoma
DLT	Dose limiting toxicity
DMSO	Dimethyl sulphoxide
DNA	Deoxyribonucleic acid
DOR	Duration of response
EAS	Efficacy analysis set
ECG	Electrocardiogram
ECHO	Echocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FLU	Fludarabine
FLU-CY	Fludarabine and cyclophosphamide
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
G-CSF	Granulocyte-colony stimulating factor
HLH	Haemophagocytic lymphohistiocytosis
HTLV	Human T cell lymphotropic virus
HuCAR-19	Human CD19 CAR
IB	Investigator's Brochure
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
ID	Identification
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IFN	Interferon
Ig (A, M, G)	Immunoglobulin (A, M, G)
IHC	Immunohistochemistry
IL	Interleukin
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
irAE	Immune-related adverse event
IRB	Institutional review board
i.v.	Intravenous(ly)

Abbreviation	Definition
LPLV	Last patient, last visit
LVEF	Left ventricular ejection fraction
q1y	Once per year
MAD	Maximum administered dose
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mesoCAR	CAR T cells against mesothelin
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
OX40	Also known as tumour necrosis factor receptor superfamily 4 (TNFRSF4) and cluster of differentiation 134 (CD134)
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PIS	Patient information sheet
PR	Partial response
PT	Preferred term
QP	Qualified Person
R-CHOP	Rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone
RCR	Replication competent retrovirus
RP2D(s)	Recommended Phase II dose(s)
SAE	Serious adverse event
SAP	Statistical analysis plan
SEC	Safety Evaluation Committee
scFv	Single chain variable fragment

Abbreviation	Definition
SmPC	Summary of Product Characteristics
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TLS	Tumour lysis syndrome
TNF	Tumour necrosis factor
UK	United Kingdom
ULN	Upper limit of normal
UPENN	University of Pennsylvania
USPI	United States Prescribing Information

1 INTRODUCTION

AUTO3 is an advanced therapy investigational medicinal product (ATIMP) consisting of autologous enriched T cells retrovirally transduced to express two Chimeric Antigen Receptors (CARs) targeting cluster of differentiation (CD) 19 and/or CD22 (herein referred to as CD19/CD22 CAR). AUTO3 cells express second generation CARs in which the CD19 CAR uses OX40-ζ endodomains and the CD22 CAR uses 41BB-ζ endodomains. Both CARs are delivered from a single retroviral vector during drug product manufacture.

Since CD19 and CD22 both are pan B lymphocyte markers, AUTO3 can target B cell lymphoma such as diffuse large B cell lymphoma (DLBCL) and other lymphomas that express these antigens. In pre-clinical studies, AUTO3 efficiently lyses B cell lymphoma lines expressing both CD19 and CD22 or either antigen alone. The objectives of this Phase I/II first -in-human study (AUTO3-DB1) are to: (1) evaluate the safety profile, (2) establish (a) recommended Phase II dose(s) (RP2D[s]), and (3) in Phase II determine the preliminary anti-tumour activity of AUTO3 in patients with relapsed or refractory DLBCL and its defined subsets. AUTO3 will be administered following lymphodepletion with fludarabine (FLU) and cyclophosphamide (CY). A limited duration of consolidation or pre-conditioning with pembrolizumab, an antibody targeting the programmed cell death protein 1 (PD-1), will follow or precede AUTO3 infusion.

A summary of the nonclinical characteristics of AUTO3 are described below in Section 1.5. For the most comprehensive nonclinical information, refer to the Investigator's Brochure (IB). Details regarding AUTO3 administration and laboratory procedures are provided in the Product Handling Manual and Lab Manual, respectively.

1.1 DIFFUSE LARGE B CELL LYMPHOMA INCLUDING SUB-TYPES

Diffuse large B cell lymphoma is the most common aggressive lymphoid malignancy and accounts for 30% to 58% of newly diagnosed lymphoma cases. With standard chemoimmunotherapy, including rituximab and an anthracycline-containing regimen, approximately 67% of patients are alive without lymphoma with a median follow-up of 4 years. However, one-third of patients have disease that is either refractory to initial therapy or relapses after standard therapy. The 3-year progression-free survival (PFS) for patients who experience an early relapse after rituximab treatment is only 23% (Gisselbrecht et al. 2010). Standard of care for patients who relapse after, or are refractory to, first-line chemotherapy is salvage chemotherapy followed by high dose therapy and autologous haematopoietic stem cell transplantation (ASCT) (Philip et al. 1995) and has long-term disease-free survival (DFS) rates above 50% to 60% (Sauter et al. 2015).

Prognosis for patients who relapse after ASCT or fail initial salvage is particularly poor. In patients with DLBCL that has progressed after ASCT, median overall survival (OS) is <10 months (Vose et al. 1992, Nagle et al. 2013). Among ASCT eligible patients, 50% cannot get ASCT due to inadequate response to high dose therapy. Prognosis of patients not eligible for high dose therapy and ASCT is poor. Among patients refractory to second-line chemotherapy, <50% of patients respond to third-line chemotherapy, and few experience long-term survival (Elstrom et al. 2010, Friedberg 2011, Moore et al. 2012). The median OS of patients requiring third-line treatment is 4.4 months (Van Den Neste et al. 2016). Patients with histologic transformation of follicular lymphoma (FL) or other indolent lymphomas to DLBCL have similar OS and PFS as *de novo* DLBCL when treated similarly with rituximab based chemoimmunotherapy (Guirguis et al. 2014), but those who are resistant to initial

therapy or who relapse following initial therapy, do poorly. When treated with salvage chemotherapy and ASCT, the responses and outcomes for transformed indolent lymphoma patients are poor and similar to those with *de novo* DLBCL (Kuruvilla et al. 2015, Sorigue et al. 2016). Interestingly, therapies inducing complete remission (CR) in aggressive non-Hodgkin's lymphoma (NHL) such as DLBCL result in significantly improved OS (Van Den Neste et al. 2016). Therefore, more effective therapies that can induce CR in NHL subtypes are urgently required.

CD19, a cell surface biomarker that is highly expressed on the surface of almost all B cell lymphomas, is an attractive target for therapeutic intervention. Successful results have been reported with blinatumomab, a bi-specific T cell engaging antibody targeting CD19, in NHL (Viardot et al. 2016). Immunotherapies with CAR T cells targeting CD19 antigen have also shown promising efficacy (Kochenderfer et al. 2015). A limitation of this single antigen therapeutic approach is tumour escape due to antigen downregulation, which has been well demonstrated in acute lymphoblastic leukaemia (ALL) (Lee et al. 2014, Maude et al. 2014, Topp et al. 2014, Shah et al. 2016, Turtle et al. 2016) and recently in lymphoma (Brudno and Kochenderfer 2016). Since CD22 is also selectively expressed on normal and malignant B cells (Polson et al. 2010), targeting both CD19 and CD22 simultaneously is likely to be more effective and prevent development of CD19 or CD22 negative tumour escape.

Another observation with CD19 CAR therapy in DLBCL and other lymphomas is that partial responses (PR) are not durable and only 70% of CRs are durable, similar observation also noted with primary mediastinal B cell lymphoma and transformed FL (Neelapu et al. 2016). In addition, a quarter of DLBCL patients do not respond to CAR therapy. Therefore, approaches targeting reactive or *de novo* resistance to T cell therapy will likely improve CAR T cell therapy efficacy.

Increase in programmed cell death ligand 1 (PD-L1) expression by tumour cells plays a crucial role in tumour's adaptive resistance to the immune response and likely plays a role in *de novo* and acquired resistance to CAR immunotherapies. The PD-L1 mediates its anti-immune response through interaction with PD-1, which is typically expressed by T cells. The PD-L1 protein is expressed on 10% to 30% of DLBCL tumours (Andorsky et al. 2011, Chen et al. 2013, Rossille et al. 2014, Kiyasu et al. 2015, Dong et al. 2016) and the percentage of tumours expressing PD-L1 increases to ~50% in patients with refractory, treatment-resistant DLBCL (Vranic et al. 2016). Recently, a patient whose tumour was PD-L1 positive and had progressive disease after CD19 CAR T cell therapy was administered the anti-PD-1 antibody pembrolizumab on Day 26 following CAR T cell infusion which resulted in clinically significant anti-tumour response (Chong et al. 2016). Similar observations have been noted in ALL patients treated with blinatumomab (Kohnke et al. 2015, Feucht et al. 2016). Using an anti-PD-1 antibody, such as pembrolizumab, can reverse such immune inhibition and may also decrease PD-1-mediated CAR T cell exhaustion (Cherkassky et al. 2016). In addition to the baseline PD-L1 expression seen in patients with DLBCL, there is evidence that DLBCL can upregulate PD-L1 as a defence mechanism against CAR T cell attack (Neelapu et al. 2017) . Long-term follow-up from the ZUMA1 study of CD19 CAR in patients with NHL demonstrated that 62% (13/21) of available biopsies showed PD-L1 expression at progression.

In this study, we will evaluate the safety of AUTO3 alone and with an anti-PD-1 antibody, pembrolizumab.

1.2 CD19 AND CD22 AS TARGETS FOR THERAPY

CD19 is a cell surface biomarker for lymphocytes that is present on most B cell malignancies, including B cell NHL and ALL. Its selective expression on the B cell lineage make it an excellent target for immunotherapy approaches avoiding toxicity to the non-lymphoid tissues. Clinical studies have shown that CAR T cells directed against CD19 are highly efficacious in treating relapsed/refractory B lineage ALL, with 70% to 90% of patients achieving CR (Davila et al. 2014, Lee et al. 2014, Maude et al. 2014, Turtle et al. 2016). However, not all patients respond and CD19-negative escape relapses have been observed (Lee et al. 2014, Maude et al. 2014, Turtle et al. 2016), therefore, additional targets are needed. Like CD19, CD22 is a cell surface biomarker for B lymphocytes that is selectively expressed on normal B cells and most B cell malignancies, including >90% ALL (Shah et al. 2015), DLBCL, and various other NHL subtypes (Mason et al. 1987).

Importantly, CD22 expression has been shown to be maintained in ALL that has lost CD19 expression, making CD22 CAR T cells a potential combination or follow-on therapy after CD19 CAR T cell therapy. Recently CD19-negative tumour escape has also been reported in lymphoma (Brudno et al. 2016). Since CD19 and CD22 are cell surface markers for lymphocytes that are present on most B cell malignancies, a combination of two CARs targeting CD19 and CD22 is likely to be a promising therapeutic approach for B cell malignancies addressing the issue of antigen escape.

1.3 CLINICAL EXPERIENCE WITH CAR T THERAPIES IN DLBCL

CD19 CAR T cell therapies for DLBCL have demonstrated efficacy in clinical trials (Brentjens et al. 2003, Cooper et al. 2003, Hoyos et al. 2010, Jensen et al. 2010, Kochenderfer et al. 2010, Porter et al. 2011, Savoldo et al. 2011, Kochenderfer et al. 2012). While the CD19 CAR construct used by each institution differs in several respects, including CAR design, T cell activation, transduction methods, and cell doses, the net observed effects remain consistent with regards to the safety and efficacy of CD19-targeted CAR T therapies. Data from some of the key CD19 CAR studies have been summarised in IB Section 2.4 and briefly below.

National Cancer Institute (NCI) studies: One NCI study using a CD19 (CD28-ζ endodomain) CAR reported CR in four of seven evaluable patients with chemotherapy-refractory DLBCL; three of these four CRs were ongoing, with durations ranging from 9 to 22 months at the time of the report (Kochenderfer et al. 2015). In another study, with a fully human CD19 CAR (HuCAR-19) in lymphoma, 86% objective response rate was observed in the nine patients treated. Three patients experienced Grade 3 cytokine release syndrome (CRS) and one experienced significant neurological toxicity (encephalopathy); however, all toxicities resolved fully in all patients. Interestingly, the authors reported, for the first time in lymphoma, a patient with complete loss of CD19 expression by lymphoma cells after two HuCAR-19 T cell infusions, which was associated with lymphoma progression (Brudno et al. 2016).

University of Pennsylvania (UPENN) studies: In a study in adults with relapsed/refractory NHL with a CD19 CAR with 41BB-ζ endodomain (CTL019) following Investigators' choice of lymphodepleting chemotherapy. Eighteen of 28 evaluable patients achieved objective response. Six of 14 patients with DLBCL and ten of 14 patients with FL achieved a CR (Schuster et al. 2017).

Another study with CTL019 in DLBCL reported at the American Society of Hematology (ASH) 2016 meeting, among the 13 patients that were evaluable for response at 3 months post-CTL019, overall response rate (ORR) was 52%. Complete response rate at 3 months was 38%. To date, no patient achieving CR has relapsed. At median follow-up (23.3 months for responding patients), 85.7% (95% CI: range 33.7% to 97.9%) maintained response (Schuster et al. 2016). This study was updated and published in the New England Journal of Medicine in 2019 and showed an ORR of 52% and CR of 40% in 93 patients who received infusion (Schuster et al. 2019).

Juno Therapeutics studies: A study in NHL with a CD19 CAR with 41BB-ζ endodomains (JCAR017) was reported at the ASH meeting in 2016. In the DLBCL subgroup, overall response rates were 82% (nine of 11 patients), CR rate was 73% (eight of 11 patients), and PR rate of 9% (one of 11 patients) and 18% (two of 11 patients) had progressive disease at the time of post-treatment assessment on Day 29. One DLBCL patient in CR had a parenchymal brain lesion in the right temporal lobe that also completely resolved. Of note, this patient had no CRS or neurotoxicity (NT) associated with JCAR017 treatment. Three patients had low grade CRS (21%, two Grade 1; one Grade 2) and none required treatment with tocilizumab. Two of the 14 treated patients (14%) had NT: one Grade 4 encephalopathy and one Grade 4 seizure. Two deaths were seen in the DLBCL group which were due to disease progression (Abramson et al. 2016). At a subsequent investor update at the 35th Annual J.P. Morgan Healthcare Conference on 10 January 2017, it was reported that at 1 month, the CR rate was 60% (12 of 20 patients) and decreased to 42% (eight of 20 patients) at 3 months. Overall, the study reported a durability rate of 66% for CRs at 3 months, similar to the durability rate reported with Kite's axicabtagene ciloleucel in a similar patient population (Neelapu et al. 2016).

Kite Pharma studies: The ZUMA-1 study in DLBCL with axicabtagene ciloleucel, was the basis of approval of this product by the Food and Drug Administration (FDA) in October 2017. Of the 101 patients treated, the ORR was 82% and median time to response was 0.9 months, with 54% of patients achieving a CR. Response durations were longer in patients who achieved CR. Forty percent of the patients continue to be in CR with a median follow-up of 15.4 months (Neelapu et al. 2017).

Cytokine release syndrome was reported in 94% of the patients, most were mild, with 13% being ≥Grade 3. Neurotoxicity occurred in 87% of patients, Grade 3 or higher in 31% of patients. Most NT (98%) occurred within the first 8 weeks of infusion (YESCARTA Prescribing Information 2017).

Safety: The major toxicities observed after CD19 CAR-positive T cell transfusion are B cell depletion, CRS and NT. B cell aplasia arises because of the expression of CD19 or CD22 on all cells committed to the B lineage, therefore this population is eliminated in the presence of effective CD19- or CD22-reactive CAR T cells. The duration of B cell aplasia is a useful surrogate of persistence of CAR T cells and depends on the CAR construct employed. CD19/CD22 CARs employing both an OX40 and a 41BB domain may mediate B cell aplasia for durations similar to those seen with 41BB containing CD19 CARs i.e. up to 24 months or longer (Grupp et al. 2014), whereas durations of 1 to 3 months are more likely following therapy with CD28-containing CAR T cells (Davila et al. 2014, Lee et al. 2014). Persistent B cell aplasia could result in increased risk of infection; however, long-term immunoglobulin (Ig) replacement can mitigate infectious complications. Management of CRS has significantly improved with use of guidelines and early use of tocilizumab, but management of NT still needs further improvement. However, close monitoring, use of appropriate doses and use of steroids have improved the management of NT (Brudno and Kochenderfer 2016).

1.4 PD-1/PD-L1 AXIS IN CAR T CELLS AND LYMPHOMA AND THE ROLE OF ANTI-PD-1 THERAPY

1.4.1 CAR T Cell Exhaustion

It is well accepted that the anti-tumour efficacy of adoptively-transferred T cells requires efficient expansion and persistence *in vivo* (Kowolik et al. 2006). Cells expressing CARs can show limited expansion, persistence, and anti-tumour efficacy. T cell exhaustion is a major factor limiting anti-viral and anti-tumour responses in the setting of chronic antigen exposure (Ahmadzadeh et al. 2009, Kao et al. 2011). Exhausted T cells have low proliferative and cytokine producing capacities, high rates of apoptosis, and express high levels of inhibitory receptors such as PD-1, TIM-3, and LAG-3 (Virgin et al. 2009, Kao et al. 2011). The phenomenon of CAR T cell exhaustion, both functionally and in actual numbers, is well described in pre-clinical literature.

In pre-clinical studies, overexpression of PD-1 in CAR T cells upon antigen stimulation is often observed and this can lead to an exhausted or hypofunctional phenotype (John et al. 2013, Moon et al. 2014, Gargett et al. 2016). In an anti-GD2 CAR T model, repeated antigen stimulations lead to PD-1 overexpression, reduced cytokine production by CAR T cells and activation induced cell death. Repeated antigen stimulation also reduced the number of viable GD2 CAR T cells. Administration of pembrolizumab, an anti-PD-1 antibody, restored cytokine production, viability of CAR T cells, and enhanced tumour killing (Gargett et al. 2016). In an anti-Her2 CAR T model, antigen stimulation led to overexpression of PD-1 on Her2 CAR T and administration of an anti-PD-1 antibody increased tumour killing by Her2 CAR T (John et al. 2013). The significance of PD-1 expression and CAR T cell hypofunction was further demonstrated in another pre-clinical model involving CAR T cells against mesothelin (mesoCAR). Stimulated mesoCAR T cells exhibited elevated PD-1 expression, reduced cytokine production, and reduced tumour killing. Administration of PD-L1 inhibitors restored cytokine production and tumour killing (Moon et al. 2014).

Clinical examples of PD-1 upregulation have also been observed in CAR T cells isolated from patients. Kochenderfer et al showed that PD-1 expression on CD19 CD4+ CAR T cells increased in 8/11 DLBCL patients treated with CD19 directed CAR T cells (Kochenderfer et al. 2015). In patients with B lymphoblastic leukaemia treated with tisagenlecleucel, it has also been postulated that CD19-positive relapses are largely due to early CAR T cell loss (Li et al. 2018). T cell exhaustion or activation-induced CAR T cell death has been suspected to contribute to poor persistence of CAR T cells, and inhibiting the PD-1/PD-L1 checkpoint axis may decrease T cell exhaustion, thereby improving CAR T cell function and persistence (Li et al. 2018).

1.4.2 Role of PD-L1/PD-1 Axis on Cancer Immune Suppression

Programmed cell death ligands 1 and 2 (PD-L1 and PD-L2) are expressed on tumour cells in numerous cancers, including haematological malignancies such as myeloma, NHL and Hodgkin's lymphoma (Okazaki and Honjo 2007, Andorsky et al. 2011, Chen et al. 2013, Atanackovic et al. 2014, Kiyasu et al. 2015). Increased PD-L1 expression by tumour cells is a crucial part of the tumour's adaptive resistance to the immune response and likely plays a role in CAR immunotherapies as well. PD-L1 expression results in suppression of tumour immunity through a number of different mechanisms including induction of T cell apoptosis, T cell anergy and functional exhaustion, and interleukin (IL)-10 production (Chen and Han 2015).

Importantly, PD-L1 acts as a molecular shield on tumour cells, as binding of PD-1 on cytotoxic T cells to PD-L1 on tumour cells inhibits the T cells' cytolytic activity (Chen and Han 2015)

1.4.2.1 PD-L1 Expression in DLBCL De Novo

In DLBCL, 10% to 30% of tumours express PD-L1 (Andorsky et al. 2011, Chen et al. 2013, Rossille et al. 2014, Kiyasu et al. 2015, Dong et al. 2016, Menter et al.). PD-L1 is expressed on both select DLBCL tumour cells (11%) and on tumour-infiltrating non-malignant cells (15.3%) (Kiyasu et al. 2015). The percentage of tumours expressing PD-L1 increases to approximately 50% in patients with refractory, treatment-resistant DLBCL (Vranic et al. 2016). PD-L1 expression in DLBCL has been reported to have prognostic value (Kiyasu et al. 2015, Dong et al. 2016) and is an independent indicator of poor prognosis. Although PD-L1 is associated with a poor prognosis, blockade of the PD-1/PD-L1 axis in DLBCL has not translated into an effective therapy. In a large Phase II trial in patients with relapsed/refractory DLBCL, nivolumab only resulted in an ORR of 10% in transplant-eligible patients and 3% in transplant-ineligible patients (Ansell et al. 2019). Thus, it has been conclusively demonstrated that PD-1/PD-L1 inhibitors essentially have no activity in patients with relapsed/refractory DLBCL.

1.4.2.2 Impact of CAR T Cell Immunotherapy on PD-L1 Expression in DLBCL

In addition to the baseline PD-L1 expression seen in a quarter of DLBCL patients, there is evidence that other tumour cells also use PD-L1 checkpoint upregulation as a defence mechanism against CAR T cell attack. This has also been reported in a CD19-CAR T cell (axicabtagene ciloleucel) trial in DLBCL (ZUMA-1 study; (NCT02348216 2015)). In the ZUMA-1 study, gene expression profile comparisons of pre- and post-axicabtagene ciloleucel treatment biopsies showed profound changes in gene expression within the tumour environment after infusion, including immune checkpoints PD-L1 and LAG3 upregulation (Galon et al. 2017). Post-progression biopsies were available in 21 patients of whom 62% had PD-L1 expression at progression (Neelapu et al. 2017).

1.4.3 Effect of PD-1/ PD-L1 Axis Blockade on CAR T Cell Immunotherapy in Lymphoma

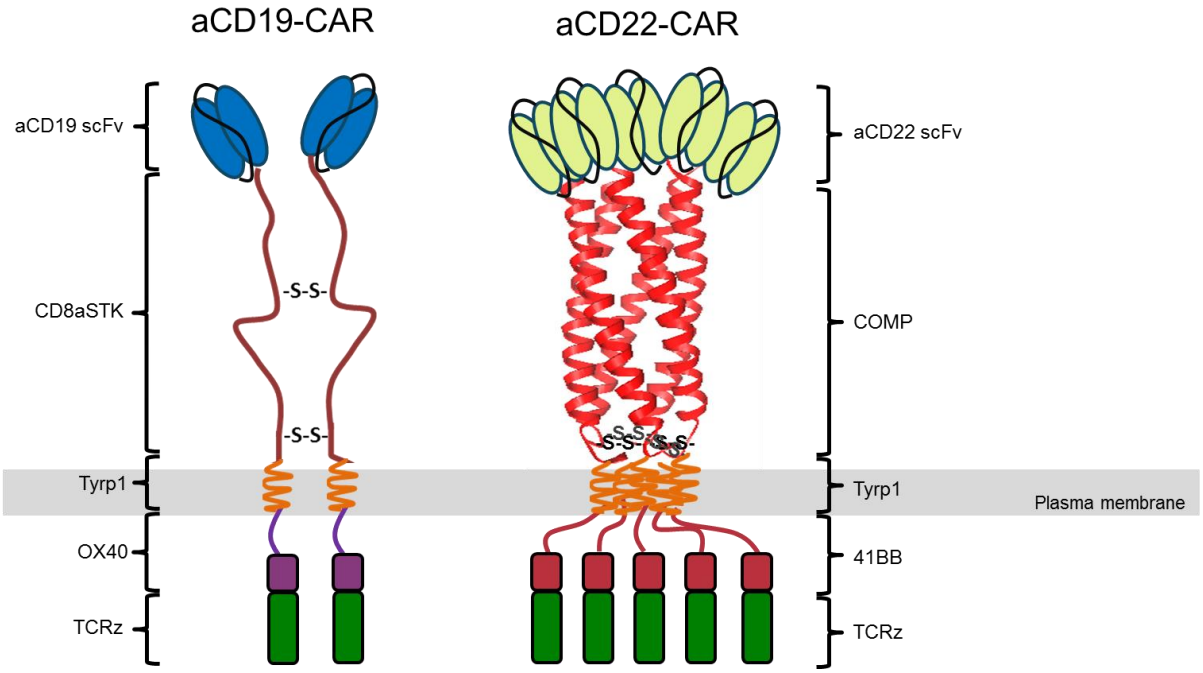
This expression of PD-L1 on DLBCL cells and activation-dependent expression of PD-1 on CAR T cells after infusion has led to the hypothesis that PD-1 pathway blockade may augment the activity of CAR T therapy and result in improved clinical outcomes in DLBCL. Combining CAR T cell therapy with immune checkpoint blockade therapy targeting the PD-1/PD-L1 interaction could thus improve efficacy and overcome resistance following engineered T cell therapy for cancer patients in general and for DLBCL more specifically. Multiple clinical trials investigating the combination of CD19-specific CAR T cells and PD-1 or PD-L1 blockade are ongoing (Yoon et al. 2018). Notably, the most clinically advanced CD19 CAR T therapies, axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel (JCAR017) are now being investigated in combination with an anti-PD-1/PD-L1 antibody (refer to Section 4.6).

The totality of data from these studies suggests that the combination of CD19 CAR T cells with PD-1/PD-L1 antibodies is well tolerated and safety is comparable to that of CD19 CAR T cells alone; specifically, no worsening of CRS or NT has been observed. With the administration of PD-1/PD-L1 antibodies the CAR T cells may have better expansion and persistence thus possibly leading to deeper and more durable responses.

1.5 DESCRIPTION OF AUTO3- CD19/CD22 CAR-POSITIVE T CELLS

AUTO3 is a novel cellular gene therapy, consisting of autologous patient T cells, genetically modified to express two CARs targeting CD19 and CD22 from a single construct. The active substance is the genetically modified T cells, named CD19/CD22 CAR-positive T cells. To generate AUTO3, autologous T cells are isolated, activated and transduced to express both CD19 and CD22 CARs on the same cell (Figure 1), expanded and frozen down. The CD19/CD22 CAR construct utilises humanised forms of the murine anti-CD19 antibody HD37 and the murine anti-CD22 antibody LT22 converted into a single chain variable fragment (scFv) format. The protein structure of each of the CD19 and CD22 CARs consists of the binding domains (scFv) followed by a spacer derived from either the dimeric human CD8a for the CD19 CAR or a pentameric coiled-coil structure from human collagen oligomeric matrix protein for the CD22 CAR. Both CARs contain a human tyrosinase-related protein-1 (Tyrp-1) transmembrane domain. In a second-generation format, the CD19 CAR construct uses OX40-ζ endodomains and the CD22 CAR uses 41BB-ζ endodomains.

Figure 1: Structure of the Proteins Expressed on the Surface of AUTO3 Cells



The CD19 CAR and CD22 CAR are type I transmembrane proteins. The anti-CD19 CAR is shown on the left. Humanised HD37 derived scFv recognises CD19 at the extreme amino-terminus, and it is connected to the CD8α stalk, transmembrane and anchor. The intracellular endodomains are composed of co-stimulatory OX40 and CD3-ζ (TCRz). The anti-CD22 CAR is shown on the right. Humanised LT22 derived scFv recognises CD22 at the extreme amino-terminus and is connected to the pentameric α-helical coiled-coil multimer-forming domain of cartilage oligomeric matrix protein (COMP) and transmembrane anchor. The intracellular endodomains are composed from 41BB-ζ and CD3-ζ (TCRz).

1.6 SUMMARY OF NONCLINICAL STUDIES

Further details regarding AUTO3 can be found in the IB.

1.6.1 In Vitro and In Vivo Pharmacology

Surface plasmon resonance was used to evaluate binding kinetics between the humanised Fc binding domains of CD19-CAR (HD37) and CD22-CAR (LT22) and their respective ligands.

Binding affinities of 1.09 and 32 nM were measured between CD19 and CD22 respectively. The kinetic binding parameters were consistent with the parent mouse-derived binding domains and those of other scFv of CAR T cells currently being clinically tested.

The functionality of the CD19/CD22 CAR construct was compared to that of individual CD19 and CD22 CAR constructs. Target cells used were SupT1 cells (a human T lymphoblast cell line) naturally negative for CD19 and CD22 (negative control); SupT1 cells engineered to express either CD19 or CD22 or Raji cells (a human B cell line) naturally expressing both CD19 and CD22. The specificity of the CD19 CAR was confirmed by restricted cytotoxicity toward the CD19-positive SupT1 cells and Raji cells only. Likewise, co-cultures with CD22 CAR showed restricted cytotoxicity to CD22+ SupT1 cells and Raji cells only. Similar levels of cytotoxicity were observed using the CD19/CD22 CAR construct and the CD19 and CD22 single CAR constructs, demonstrating no loss of function of the CD19 and CD22 CARs when expressed on the same construct. Similar results were observed when measuring interferon (IFN)-γ, tumour necrosis factor (TNF)-α and IL-2 secretion and proliferative responses after co-culture of CD19-positive, CD22-positive and dual-positive target cells with CAR T cells confirming the functionality of the CD19 and CD22 CARs.

The ability of CD19/CD22 CAR-positive T cells to kill CD19-escape variants was confirmed in co-cultures using mixtures of Raji cells and CD19-knockout Raji cells. Similar levels of cytotoxicity were detected against the mixed culture as with wild-type Raji cells only, demonstrating that T cells transduced with the CD19/CD22 CAR constructs can effectively destroy CD19-negative, CD22-positive targets. Likewise, CD19/CD22 CAR-positive T cells could secrete IFN-γ and IL-2 and proliferate in response to targets expressing either antigen. These data demonstrate that CD19/CD22 CAR-positive T cells specifically recognise target cells expressing both CD19 and CD22 antigens and should effectively delete CD19-negative escape variants. CD19/CD22 CAR-positive T cells were tested in an *in vivo* tumour xenograft mouse model using non-obese diabetic severe combined immunodeficiency gamma mice. Mice received wild-type Raji cells i.v. and 3 days later, mice were stratified between treatment groups to equalise tumour burden. Treated animals were given i.v. CD19/CD22 CAR-positive T cells or mock-transduced T cells. Assessment of disease burden 16 days after tumour cell injection demonstrated significant retardation of tumour growth in all mice receiving CD19/CD22 CAR T cells compared to the control group. Analysis of the bone marrow (BM) and spleens of mice treated with CD19/CD22 CAR-positive T cells reveal complete abrogation of tumour cells ($P<0.01$) and expansion of CAR T cells ($P<0.01$), compared to controls.

To determine if treatment with an anti-PD-1 antibody may affect CAR T cell performance, the effect of addition of an anti-PD antibody to co-cultures of CD19/CD22 CAR T cell and Raji tumour cells was also assessed. No differences in CAR T cell cytotoxicity, proliferation, or cytokine production were observed in cultures containing the anti-PD-1 antibody compared to activity of CAR T cells alone. In a second study, an *in vitro* system was established to mimic the potential exhausted cellular phenotypes observed during tumour-mediated downregulation of T cell responses. To this end, CAR T cells were pre-activated in order to increase the surface expression of PD-1 and target cells were transduced to constitutively express PD-L1. Co-culture of pre-stimulated CD19/CD22 CAR T cells with PD-L1-positive target cells showed decreased cytotoxicity and cytokine production compared to co-culture with wild-type target cells. However, addition of anti-PD-1 to these co-cultures restored cytotoxicity and cytokine production to levels observed for co-cultures with wild-type target cells. These data suggest that co-treatment with an anti-PD-1 antibody could potentially enhance CD19/CD22 CAR T cell functionality in the context of tumour-mediated immunosuppression. Anti-PD-1 antibodies

such as pembrolizumab can therefore overcome CAR T cell exhaustion, and this serves as a rationale for pembrolizumab to be incorporated into the pre-conditioning regimen of this current study. For further details, see the IB.

1.6.2 Toxicology

A Good Laboratory Practice tissue cross-reactivity study was conducted to characterise the potential cross reactivity of humanised HD37 (CD19-CAR) and LT22 (CD22-CAR) binders by immunohistochemistry (IHC). A panel of 42 different frozen human tissues and blood smears (3 donors per tissue) was evaluated. The optimised IHC assay was validated in an initial study and two different concentrations of HD37 (0.1 and 0.5 µg/mL) and LT22 (0.2 and 1 µg/mL) were investigated.

LT22 and HD37 binders elicited prominent membrane (with variable cytoplasmic) staining in scattered mononuclear cells, within lymphoid aggregates/infiltrates and/or within inflammatory foci in several tissues, including adrenal gland, oesophagus, liver, lung, ovary, oviduct, pancreas, prostate, parathyroid gland, parotid salivary gland, ureter, urinary bladder, uterus cervix and endometrium.

Cell morphology and distribution were generally consistent with lymphocytes. HD37 binders also produced minimal to marked membrane/cytoplasmic staining in numerous mononuclear cells within the lamina propria throughout the digestive tract, from stomach to rectum. This staining pattern was not seen with the LT22 binder. The labelled cells may represent lymphocytes but other cell types such as dendritic cells and/or macrophages cannot be ruled out.

No positive staining was observed in the brain (cerebellum and cerebral cortex), spinal cord, eye, heart, blood vessel, kidney, nerve, pituitary gland, placenta, skeletal muscle, skin, testes, and thyroid gland.

In summary, humanised LT22 and HD37 binders produced prominent membrane (with variable cytoplasmic) staining in follicular compartments of lymphoid organs and in scattered mononuclear cells, within lymphoid aggregates/infiltrates and/or within inflammatory foci in many other tissues. Based on morphology and distribution, the targeted cells were most consistent with lymphocytes. Importantly, binding of both antibodies was restricted to haemopoietic tissues and lymphoid organs with no binding to other tissues, limiting the likelihood of "on target, off tumour" toxicity.

1.7 SUMMARY OF CLINICAL STUDIES

The current study is the first in human study of this ATIMP, AUTO3, in the DLBCL patient population and the study has been initiated in the UK and USA.

As of 30 October 2020, 49 patients had been treated with AUTO3. The median (range) age was 59 (27 to 83) years and median number of prior therapies was 3 (1 to 11). Overall, 69% of patients had DLBCL NOS, 22% had Transformed/Indolent Lymphoma, and 6% of patients had High Grade B Cell Lymphoma and 2% had Primary Mediastinal Large B Cell Lymphoma. No DLT was observed during dose escalation. Treatment emergent AEs that occurred in > 20% of patients were neutropenia (59%), anaemia (51%), thrombocytopenia (47%), CRS (35%), pyrexia (27%), and fatigue (25%). Treatment emergent AEs ≥Grade 3 that occurred in >20% of patients were neutropenia (57.1%), thrombocytopenia (37%), and anaemia (41%).

The majority of SAEs were haematological or associated with infections and largely reversible. Across all dose levels, there were 17 cases (35%) of CRS in total (10 cases of Grade 1 CRS, 6 cases of Grade 2 CRS and 1 case of Grade 3 CRS) (Table 1). No prophylactic measures of any kind were used. The median time to CRS was 2 days (range 1-36), while the median duration of CRS was 3 days (range 1-19). Eight patients received tocilizumab (16%) and no patients received steroids.

Table 1 Cases of Cytokine Release Syndrome by Grade and Dose Level

	Total (N=49)	50 x 10^6 AUTO3 (N=7)	150 x 10^6 AUTO3 (N=16)	300 x 10^6 AUTO3 (N=10)	450 x 10^6 AUTO3 (N=16)
All Grades	17 (35%)	1 (14%)	4 (25%)	2 (20%)	10 (63%)
Grade 1	10 (20%)	1 (14%)	2 (13%)	2 (20%)	5 (31%)
Grade 2	6 (12%)	0	1 (6%)	0	5 (31%)
≥ Grade 3	1 (2%)	0*	1 (6%)	0	0

There were 3 cases (6%) of neurotoxicity/ICANS, two of which were ≥ Grade 3. All 3 cases of neurotoxicity/ICANS occurred in the setting of disease progression without detectable CAR T cells in peripheral blood and were associated with confounding factors such as sepsis, metabolic acidosis, and narcotic use.

A total of 43 patients were evaluable for efficacy (PET + disease prior to pre-conditioning). The ORR and CRR were 65% and 51%. Among patients receiving 450 x 10^6 AUTO3, the CRR was 73% (n=15). The PFS estimate at 6 months was 40.1% (20.2, 59.2).

In the outpatient cohort, 5 of 17 patients (39%) dosed at the clinical cut-off were subsequently admitted due to AEs (febrile neutropenia and CRS). In the 5 patients admitted, the median time from infusion of AUTO3 to hospitalisation was 2 days (min-max; 2-3 days). The median duration of hospitalisation was 5 days (range 1-9 days). Outpatient administration was considered feasible.

In addition, AUTO3 has also been evaluated in a separate study in paediatric and young adult patients with relapsed/refractory ALL (AUTO3-PA1). AUTO3-PA1 was a multi-center, single-arm study that evaluated preliminary safety and efficacy of AUTO3 in this patient population. The study was initiated on 28-Jul-2017 in the United Kingdom (UK) and the last patient visit (and last visit for the study) was completed on 18-May-2020.

As of the data cut-off (29-Jul-2020), 23 paediatric and young adult patients with relapsed/refractory B cell ALL were consented to enter the study and 15 patients were infused with AUTO3 in Phase I. The median age of these 15 patients was 8 years (range: 4 to 16) with more male than female patients infused with AUTO3 (73.3% male, 26.7% female). All 15 patients who were infused had a minimum of 4 weeks follow-up and therefore completed the DLT observation period. No AUTO3 related deaths were observed and no DLTs were reported. The most common Grade ≥3 AEs were pyrexia (7 patients; 46.7%), anaemia (6 patients; 40%), and febrile neutropenia (6 patients; 40%). Eleven patients (73.3%) had Grade 1 CRS and 1 patient had Grade 2 CRS (6.7%), no Grade 3 or higher CRS (Lee Criteria; Lee et al. 2019) was seen. Five patients (33.3%) experienced neurotoxicity, 4 patients had Grade 1 and 1 patient (6.7%) had Grade 3 encephalopathy that was considered likely related to prior intrathecal methotrexate. No patients required intensive care unit admission.

Thirteen of 15 treated patients responded to the treatment, regardless of disease burden, cytogenetic risk factors, number of prior lines of therapy or AUTO3 dose. The rate of complete

morphological and molecular remission was 87% (13/15 patients) in this patient population. Two patients did not respond to AUTO3 treatment. As of the cut-off date (29-Jul-2020), 9 patients ultimately had morphological relapse. The majority of the relapses (6 of 9 patients) were CD19 positive/CD22 positive disease associated with a lack of long-term CAR T cell persistence.

1.8 OVERALL RATIONALE FOR THE STUDY

Despite these major advances, most cases of relapsed/refractory DLBCL remain incurable with the currently established therapy modalities. A considerable number of DLBCL patients will ultimately experience a final tumour relapse without an additional, effective treatment option. Novel immunotherapies such as CAR T cell therapies hold promise for significant improvement in the overall outcome of patients with DLBCL. CD19 CAR-positive T cells in clinical development for the treatment of B lineage malignancies have demonstrated significant efficacy in clinical trials. The major causes of treatment failure after CD19 CAR T cell therapy include CD19-negative escape variants, non-persistence of CAR T cells and potentially reactive upregulation of PD-L1 checkpoint by tumour cells. In contrast to targeting a single antigen expressed on lymphoma cells, targeting two antigens (CD19 and/or CD22) with the same CAR T cell is likely to be more advantageous. We hypothesise this will prevent tumour cell escape by target antigen down-regulation and significantly enhance the overall efficacy. Further, AUTO3 has also been engineered to be more effective with the incorporation of both OX40 and 41BB-ζ co-stimulatory signals and utilises humanised antigen binding domains in both CARs, hence reducing the risk of immune-mediated rejection. Furthermore, consolidation therapy with a short course (3 doses) of anti-PD-1 antibody will help overcome any resistance due to *de novo* or reactive upregulation of PD-L1 checkpoint by the tumour cells. Lastly, pre-conditioning with anti-PD-1 antibody on Day -1 prior to CAR T infusion may mitigate CAR T exhaustion and lead to improved CAR T cell expansion, persistence, and function.

This Phase I/II study will assess the safety and preliminary activity of AUTO3 with anti-PD-1 antibody (pembrolizumab) consolidation or pre-conditioning, in patients with relapsed or refractory DLBCL and large B cell lymphoma subtypes.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVES AND ENDPOINTS

Primary objectives and endpoints for Phase I and Phase II of the study are presented in Table 4 and Table 5, respectively.

Table 4: Primary Objectives and Endpoints for Phase I

Objectives	Endpoints
Escalation	
To assess the safety and tolerability of AUTO3 administration with pembrolizumab.	Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.
To identify the recommended Phase II dose (RP2D[s]) and maximum tolerated dose (MTD), if an MTD exists, of AUTO3.	Frequency of dose limiting toxicity (DLT) of AUTO3.
Expansion	
To assess the safety and tolerability of AUTO3 administration with pembrolizumab in the outpatient/ambulatory care setting	Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.

DLT=dose limiting toxicity; MTD=maximum tolerated dose; RP2D=recommended Phase II dose

Table 5: Primary Objectives and Endpoints for Phase II

Objectives	Endpoints
To evaluate the clinical efficacy of AUTO3 at the RP2D(s) with pembrolizumab in Cohort 1. To assess the overall safety and tolerability of AUTO3 with pembrolizumab in Cohort 2 at the RP2D(s).	Best overall response post-AUTO3 infusion. Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.

AE=adverse event; RP2D=recommended Phase II dose; SAE=severe adverse event

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary objectives and endpoints are presented in Table 6.

Table 6: Secondary Objectives and Endpoints for Phase I and II

Objectives	Endpoints
To assess the overall safety and tolerability of AUTO3 with pembrolizumab.	Frequency and severity of all AEs and SAEs.
	Incidence and duration of severe hypogammaglobulinaemia.
To evaluate the feasibility of generating the ATIMP, AUTO3.	Proportion of patients for whom an AUTO3 product can be generated (feasibility).
To evaluate the overall clinical efficacy of AUTO3 with pembrolizumab.	Determine the CR rate following treatment with AUTO3. To evaluate clinical outcomes including DOR, PFS and OS.
To determine the expansion and persistence of AUTO3 following adoptive transfer in different lymphoma subtypes.	PCR and/or flow cytometry at a range of time points in the peripheral blood.
Duration of B cell aplasia.	Depletion of circulating B cells assessed by flow cytometry at a range of time points in the peripheral blood.

AE=adverse event; ATIMP=advanced therapy investigational medicinal product; CR=complete response; DOR=duration of response; OS=overall survival; PFS=progression free survival; PCR=quantitative polymerase chain reaction; SAE=serious adverse event

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To determine the time course and magnitude of cytokine release evaluated using an appropriate assay.
- To evaluate the effect of anti-PD-1 antibody on the time course and magnitude of cytokine release using an appropriate assay.
- To assess the duration of depletion of circulating B cells as determined by flow cytometry on the peripheral blood and correlate this with disease response.
- To assess antibody and/or T cell mediated immune responses against AUTO3.
- To characterise the relationship between the CAR T cell phenotype/genomics and persistence *in vivo*.
- Seek any relationship between parameters of activity, level of CD19 or CD22 expression (flow cytometry), tumour PD-L1 expression, and CAR T cell phenotype.
- Seek any relationship between incidence and severity of CRS, NT or other toxicity, and tumour burden, level of CD19 or CD22 expression (IHC or flow cytometry), CAR T cell phenotype, and PD-1 expression.
- To evaluate cerebrospinal fluid (CSF) for potential markers associated with NT.

3 STUDY DESIGN

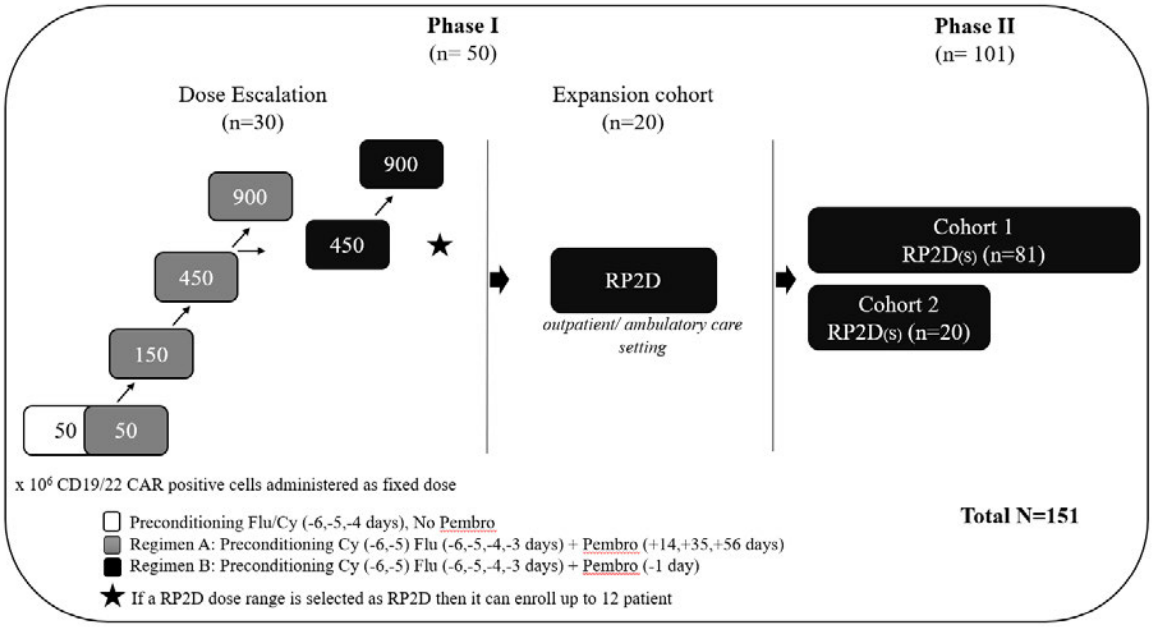
3.1 STUDY OVERVIEW

This multi-centre, single-arm study will consist of two parts, a Phase I phase and a Phase II phase:

- Phase I:
  - **Dose escalation** to identify the optimal dose of AUTO3 with pembrolizumab (doses from 50×10^6 to 900×10^6 CD19/CD22 CAR-positive T cells, administered as a single dose, will be evaluated).
  - **Expansion cohort** to assess the safety and tolerability of AUTO3 at the RP2Ds or dose range and pembrolizumab regimen identified in the dose escalation part. Approximately 20 patients with DLBCL will be treated in an outpatient/ambulatory care setting.
- Phase II: To further assess safety and anti-tumour activity at the RP2D(s) or dose range.

An overview of the study design is presented in Figure 2 below.

Figure 2: Study Design



CY=cyclophosphamide; FLU=fludarabine.
Note: Cohort 1 may include 3 to 6 patients without consolidation therapy, and 3 to 6 patients with consolidation therapy.

The study will consist of the following six stages:

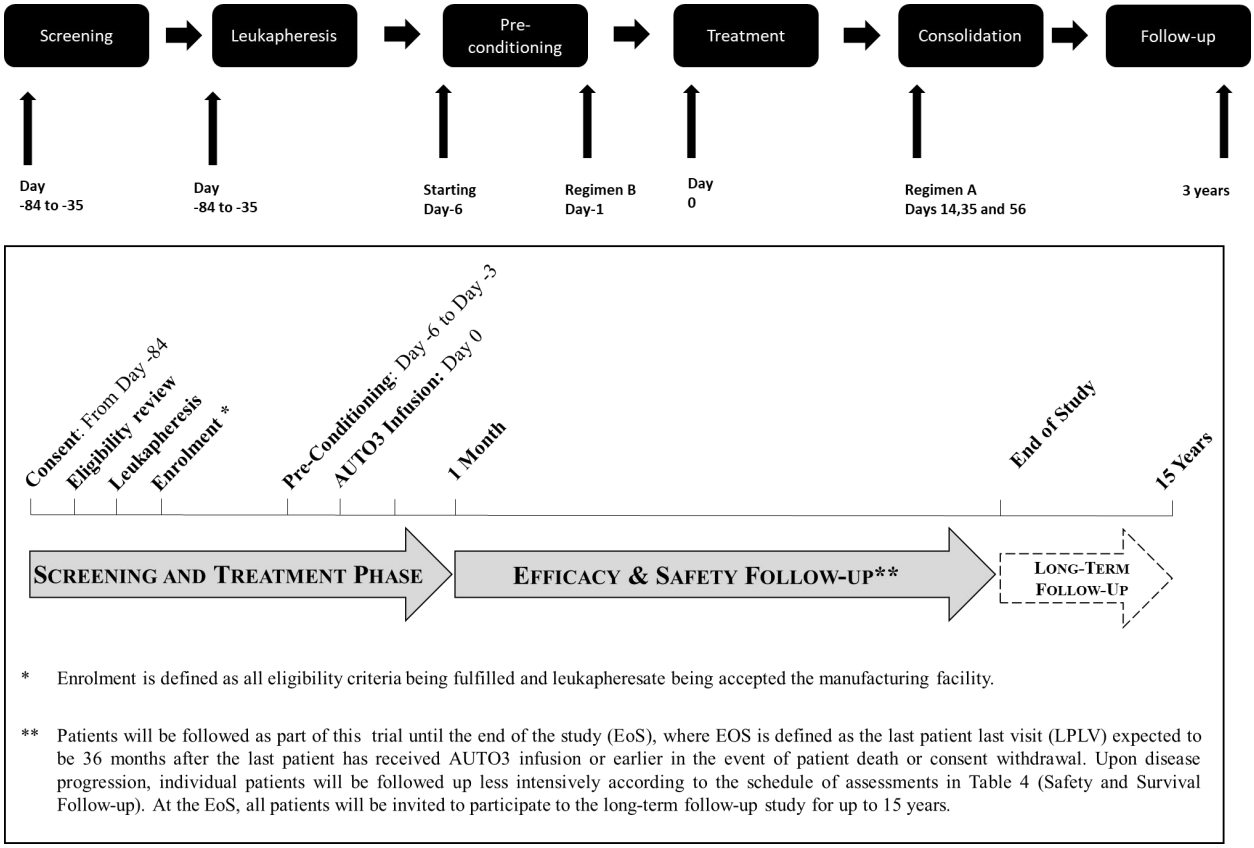
- **Screening**: After providing written informed consent for study participation, all patients will be screened for study eligibility. Eligible patients will proceed to leukapheresis.
- **Leukapheresis**: Eligible patients will undergo leukapheresis to facilitate manufacture of the ATIMP, AUTO3. Once the leukapheresate is accepted for manufacturing, the patient will be enrolled on to the study.
- **Pre-conditioning**: If sufficient AUTO3 is successfully manufactured and released, and the patients continue to meet eligibility requirements for the study, they will proceed to receive

a standard lymphodepleting pre-conditioning treatment with FLU for 4 days and CY for 2 days, to end 3 days before AUTO3 infusion. For Regimen B, pre-conditioning will include in addition to FLU and CY a single dose of pembrolizumab, 200 mg given on Day -1.

- **Treatment**: AUTO3 will be administered i.v. as a single infusion on Day 0. The treatment phase will extend from Day 0 (infusion day) until Day 28 post AUTO3 administration. Patients are expected to be monitored closely (in hospital or ambulatory care as clinically appropriate) for 10 days or longer if clinically necessary for monitoring and management.
- **Consolidation**: Provided any acute toxicities have resolved, anti-PD1 antibody (pembrolizumab, 200 mg infused over 30 min) will be administered for Regimen A on Days 14, 35 and 56 (±3 days).
- **Follow-up**: The follow-up phase will begin 1 month post AUTO3 infusion and end at the end of the study; at death or withdrawal of consent, which ever happens first.

An overview of the six study stages is presented in Figure 3.

Figure 3: Overview of the Stages of the Study



* Enrolment is defined as all eligibility criteria being fulfilled and leukapheresate being accepted the manufacturing facility.

** Patients will be followed as part of this trial until the end of the study (EoS), where EOS is defined as the last patient last visit (LPLV) expected to be 36 months after the last patient has received AUTO3 infusion or earlier in the event of patient death or consent withdrawal. Upon disease progression, individual patients will be followed up less intensively according to the schedule of assessments in Table 4 (Safety and Survival Follow-up). At the EoS, all patients will be invited to participate to the long-term follow-up study for up to 15 years.

From signing of consent until the End of Study visit, information relating to AEs, laboratory abnormalities, disease response and biomarker changes will be collected according to the AE reporting period (Section 12.3).

All patients who have received AUTO3 will be eligible for enrolment into a long-term follow-up protocol (AUTO-LT1) at the end of the study. The patients will be followed for safety

evaluation and survival for up to 15 years from their last AUTO3 infusion or until death or withdrawal of consent, which ever happens first.

3.2 PHASE I - DOSE ESCALATION

The dose escalation part of Phase I is designed to determine the RP2D(s) of AUTO3 with pembrolizumab (based on total CD19/CD22 CAR-positive T cells) in patients with DLBCL and its defined subsets. Each dose level may treat up to six patients (up to 12 patients in the dose level 1 cohort). Evaluation of a dose level with at least three patients treated at the planned dose level completing the DLT evaluation period is required prior to escalation to the next dose level. Dose escalation will follow a rolling 6 design (Skolnik et al. 2008). DLT criteria are described in Section 3.6. The dose escalation decision rules are outlined in Table 7.

Patients in the dose level 1 will receive consolidation therapy (Regimen A) with pembrolizumab from the fourth patient onwards. However, if a DLT is observed in the first three patients treated without consolidation therapy, then up to three additional patients may be treated without consolidation therapy before initiating consolidation therapy, if considered clinically necessary. A total of up to 12 patients may be treated in this cohort. All subsequent dose levels will include 3 doses of pembrolizumab consolidation therapy for patients treated on Regimen A or 1 dose of pembrolizumab as part of pre-conditioning therapy for patients treated on Regimen B.

The trial will consist of up to four dose levels (Figure 2); eligible patients will be assigned to treatment groups sequentially. The inter-patient dosing interval (inclusive of the time for pre-conditioning) for AUTO3 in Phase I will be at least **14 days**, to allow for assessment of possible toxicity, until a dose level is declared safe. After the dose level is declared safe, there will be no minimum inter-patient dosing interval required for patients treated at the same dose.

Patients treated on Regimen B will have an inter-patient dosing interval of 7 days (inclusive of pre-conditioning) as it will be opened after the dose has been declared safe on Regimen A.

Patients will be monitored for a minimum of 10 days (inpatient or ambulatory care setting), or until all AUTO3-related non-haematological toxicities have returned to Grade ≤1 or baseline, or longer as clinically necessary. The DLT evaluation period will be **28 days** after AUTO3 administration or at least 14 days after the first dose of pembrolizumab in situations where the first dose of pembrolizumab is delayed beyond Day 14.

The Safety Evaluation Committee (SEC) will meet after the first patient at every new dose level completes 14 days, to confirm continuation of enrolment to that dose level. The SEC will meet again after the third and or sixth patient in a cohort has completed the DLT assessment period. Only after a cohort is declared safe by the SEC can the next higher dose level be opened. Back filling of a cohort (maximum n=6 evaluable patients/cohort) declared safe may be undertaken in parallel to the ongoing enrolment of a higher dose level, to obtain additional biomarker and safety data. All patients will be evaluated for efficacy.

The starting dose level will be 50×10^6 CD19/CD22 CAR-positive T cells (Table 8) and if it is declared safe then the second cohort will be opened at a dose of up to 150×10^6 CD19/CD22 CAR-positive T cells and third cohort at 450×10^6 CD19/CD22 CAR-positive T cells. Once three patients have been treated at a dose of 450×10^6 CD19/CD22 CAR-positive T cells followed by pembrolizumab starting on Day 14, a new cohort will be opened at the same dose level but will receive pembrolizumab starting on Day -1 (Regimen B). Dose escalation will continue until the planned maximum administered dose (MAD) of 900×10^6 CD19/CD22

CAR positive T cells is reached. If the new consolidation schedule is not safe or well tolerated, then the earlier schedule may continue with dose escalation. A dose lower than pre-planned next higher dose may be evaluated if emerging safety data suggest that it may be more appropriate. Additionally, based on emerging data, more than one RP2D may be determined. For example, if 150×10^6 CD19/CD22 CAR-positive T cells is declared as RP2D then Phase II can be opened and in parallel further dose escalation may be continued to determine a second RP2D dose and schedule. If a higher dose (e.g. 450×10^6) is declared RP2D then based on emerging data a RP2D dose range can be declared that can extend to a lower dose (e.g. 450 to 150×10^6). If patients are treated below the planned dose level due to AUTO3 manufacturing limitations or other reasons, then those patients will not be considered evaluable for making dose escalation decisions (additional patients will be treated to meet the minimum number needed to make the dose escalation decision). However, dose escalation decisions will consider all available data, including biomarker data and the safety profile of all patients treated. No patient will be treated below 15×10^6 CD19/CD22 CAR-positive T cells.

Based on emerging data, the initiation of consolidation or pre-conditioning therapy can be delayed or withdrawn altogether. All dose escalation decisions will be made by the SEC, however the Independent Data Monitoring Committee (IDMC) may change any of these decisions.

Table 7: Rolling 6 Dose Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Escalate to the next dose level (except in dose level 1).
1 out of 3	Treat three additional patients at the current dose level for a total of six patients.
1 out of 6	Escalate to the next dose level or an intermediate dose level.
2 or more patients in a dosing cohort (up to 6 patients)	The MTD has been exceeded. Either: • Evaluate a dose lower than the current dose. • Evaluate an alternative pembrolizumab dosing schedule • Expand a prior cohort up to six patients.

DLT=dose limiting toxicity; MTD=maximum tolerated dose.
Note: The Investigators may override these guidelines if there are particular safety issues, for which moving to a higher dose is not considered appropriate.

The dose escalation decisions will be made by SEC (Section 13.1) and study could be stopped by SEC upon occurrence of any of the events described in Section 3.7.

3.3 PLANNED DOSE LEVELS

The planned dose levels are presented in Table 8. These dose levels were selected as they provide an optimum range for assessing safety, CAR T cell persistence and anti-tumour activity. The overall study range is within the dose levels assessed in other CAR T studies. Based on emerging data, intermediate dose levels may also be explored with either consolidation or pre-conditioning therapy.

Table 8: Treatment Cohorts in Phase I Dose Escalation

Dose Levels	Treatment Cohorts	Pre-conditioning (FLU-CY; Days -6, -5, -4, -3)	Total CD19/CD22 CAR-Positive T Cells (Day 0)	Regimen A: Consolidation (pembrolizumab; Days 14, 35, 56)	Regimen B: Pre-conditioning (pembrolizumab; Day -1)
Dose Level 1	Cohort 1	Yes	50×10^6	None in first three patients, then Yes	
Dose Level 2	Cohort 2A	Yes	150×10^6	Yes	
Dose Level 3	Cohort 3A	Yes	450×10^6	Yes	
	Cohort 3B	Yes	450×10^6		Yes
Dose Level 4	Cohort 4A	Yes	900×10^6	Yes	
	Cohort 4B	Yes	900×10^6		Yes
RP2D	RP2D or Dose Range Cohort	Yes	150 to 450×10^6		Yes

CAR=chimeric antigen receptor; FLU-CY=fludarabine and cyclophosphamide ; RP2D=recommended Phase II dose.

- In dose level 1, the first three patients treated at 50×10^6 CD19/CD22 CAR-positive T cells will not receive consolidation with pembrolizumab.
- Consolidation therapy with pembrolizumab (except dose on Day -1) will be administered only after any CRS has resolved to ≤Grade 1 or NT has resolved. Based on emerging data, either one or both pembrolizumab dosing regimens will be opened in Dose Level 4 (Cohorts 4A and 4B).
- On occasion, AUTO3 production may fail to generate sufficient cells for the current dose level. In this case, the patient can be treated on study but at a lower dose, however if production fails to generate $\geq 15 \times 10^6$ (approx. 0.2×10^6/kg) CD19/CD22 CAR -positive T cells, near the lowest known active dose of CD19 CAR-positive T cells (1.46×10^5 T cells/kg, approximately total dose of 10×10^6 T cells [patient UPENN chronic lymphocytic leukaemia 3, NCT0102936]), then the patient will not be treated on the study. Only patients treated at planned dose level will be evaluable for dose escalation decision making and primary efficacy analysis (± 20% window). Additional patients will be treated to meet the minimum number needed to make the dose escalation decision
- If emerging data suggest that escalation is appropriate to an intermediate dose, which is a lower than the planned dose, then it can be undertaken with Regimen A or B. Total number of patients of Phase I may also be increased if necessary.
- If emerging safety and efficacy data suggest further dose escalation is warranted, any doses higher than 900×10^6 CD/19/CD22 CAR T cells will not be undertaken without a substantial protocol amendment.

Note: The dose determination is based solely upon the genetically modified cells (i.e. CD19/CD22 CAR-positive T cells). A patient may be eligible for a planned dose level if the dose is within ±20% of the prescribed CD19/CD22 CAR-positive T cells dose.

3.4 PHASE I – Expansion Cohort

In this cohort, the safety and tolerability of AUTO3 at the RP2D or dose range will be assessed in an outpatient/ambulatory care setting following declaration of RP2D or dose range in the dose escalation part. Approximately 20 patients will be treated. There will be no inter-patient dosing interval.

Patients enrolled in this cohort will be monitored for at least 10 days in an outpatient/ambulatory care setting, or until all AUTO3-non-haematological related toxicities have returned to Grade ≤1 or baseline, or longer as clinically necessary. During the 10 days following AUTO3 infusion, the patients are monitored at a minimum every 2 to 3 days (in the UK, at least once a day evaluation by a physician or qualified designee). In addition, it is recommended for the patient to have a daily verbal communication with qualified nurse/medical personnel (phone call). Patients will also need adequate caregiver support (in line with institutional outpatient transplant guidelines). Patients enrolled or treated in this cohort can be admitted to the inpatient setting as necessary for the management of AEs or toxicity at any time. Patients can also be admitted based on Investigator discretion should they consider it inappropriate to treat or monitor an already enrolled patient in an outpatient/ambulatory setting. Physicians may also admit patients for social reasons. In all cases the reason for admission should be documented.

3.5 PHASE II

Once the RP2D(s) or dose range is/are determined, the Phase II part of the study will open with two cohorts. This part will treat approximately up to 101 patients on the RP2D(s). Cohort 1 will comprise approximately 81 patients with DLBCL subsets and transformed FL, Cohort 2 will comprise approximately 20 patients with PMBCL and DLBCL transformed from other indolent histologies. Patients treated at a dose lower than the RP2D(s) will not be evaluable for primary efficacy endpoint analysis but will be evaluable for secondary efficacy endpoints and safety analysis. Once Phase II starts, patients can be dosed simultaneously at the declared RP2D dose(s) without inter-patient intervals.

3.6 DOSE LIMITING TOXICITY

Toxicities will be graded for severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. CRS and neurological toxicity will be graded according to the American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation (ASTCT/ASBMT) consensus grading (Lee et al. 2019). DLT criteria takes into consideration the single dose nature of AUTO3 treatment (unlike repeat dose treatments of usual anti-cancer agents), the potential for differential expansion of CARs post-infusion in different patients and inclusion of consolidation or pre-conditioning therapy. As well as features inherent to CAR therapy such transient fever due to low grade cytokine release syndrome in the setting of pre-conditioning induced cytopenias/neutropenia seen in most patients and which are not necessarily classical neutropenic fevers resulting from infection.

The DLT evaluation period will be **28 days** after the infusion of AUTO3, or 14 days after the first dose of pembrolizumab, if administration of first pembrolizumab dose is delayed.

Dose limiting toxicity will be defined as:

- Any new non-haematological AE of Grade 3 or higher toxicity using the NCI CTCAE (Version 5.0), which is probably or definitely related to AUTO3 therapy, which occurs within the DLT evaluation period, and which fails to resolve to Grade 2 or better within 14 days, despite appropriate supportive measures.
- A Grade 4 CRS, NT, or cerebral oedema, or Grade 3 NT that lasts >72 hours.
- Grade >3 Disseminated Intravascular Coagulation (DIC)
- Grade >2 Infusion Reaction with AUTO3 infusion
- Any other fatal event (Grade 5) or life-threatening event (Grade 4) that cannot be managed with conventional supportive measures or which in the opinion of the SEC necessitates dose reduction or other modification to trial treatment to avoid a similar hazard in future patients. Effort should be made to perform an autopsy in case of a fatal event where the aetiology is unclear.
- Any event that in the opinion of treating Investigators and or medical monitor put patient at undue risk may also be considered a DLT.

Reporting Requirements for DLT

All DLTs must be reported to the Sponsor as serious adverse events (SAEs) within 24 hours of site staff becoming aware of them (see Section 12.3.5). The Sponsor will notify all DLTs to the SEC and IDMC.

Maximum Tolerated Dose: The MTD is defined as the highest dose level of AUTO3 at which ≤one patient out of six patients experience a DLT during the DLT evaluation period. If two or more out of six patients at a dose level experience a DLT during the DLT evaluation period, the MTD has been exceeded. If the MTD is exceeded due to a specific toxicity that can be managed with supportive care, an additional three patients may be treated at the dose level that exceeded the MTD with establishment of supportive care measures. A summary of available safety data and a description of the plans for supportive care measures with further enrolment at that dose level will be provided to Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) prior to dosing.

Maximum Administered Dose: The planned MAD for this study is 900×10^6 CD19/CD22 CAR-positive T cells in the event the MTD is not defined. The MAD may be lower based on emerging data.

Recommended Phase II Dose: The RP2D(s) will be either identical to the MTD or MAD or a lower dose level of AUTO3, selected on the basis of a cumulative review of safety, persistence of the CAR T cells and clinical activity. The RP2D(s) dose level(s), or dose cohorts (on Regimen A and or B) may be expanded to an additional six patients (total n=12) to further characterise safety. Similarly, if a RP2D dose range is selected a total of up to 12 patients may be enrolled to obtain additional safety and cellular kinetics data.

3.7 SAFETY STOPPING CRITERIA FOR THE CLINICAL TRIAL

The study could be stopped by the SEC or the IDMC upon occurrence of any of the following events:

- Unexpected and related SAEs that exposed patients participating to the study to unacceptable risk of harm *(class related toxicities such as CRS and neurotoxicities will not automatically result in stopping unless they are exposing patients to risk above what is generally seen with similar therapies).*
- Uncontrolled SAEs related to identified risks.
- The occurrence of non-haematological Grade 4 toxicity in three patients unless in the opinion of the IDMC (after review), it is likely manageable with the institution of appropriate supportive care.
- Death of a patient at any time after therapy that is definitely related to CAR T cell therapy.
- The occurrence of a second malignancy at any point after therapy that is definitely related to the CAR T cell therapy.

The study may be restarted after appropriate preventive or management guidelines have been instituted and a substantial protocol amendment has been approved by the regulatory authorities and ethics committees.

3.8 STUDY DURATION

The total study duration is estimated to be approximately 7 years from first patient enrolled to the end of the study. The end of the study (EOS) is defined as the LPLV expected to be 36 months after the last patient's AUTO3 dose or earlier in the event of patient death or consent withdrawal.

In the event of disease progression prior to the end of the study, patients will continue to be monitored for safety and survival in order to collect Health Authority requested data (e.g. delayed AEs) until the end of the study or until time of early withdrawal or death. The survival follow-up can be conducted via telephone contact if necessary.

3.9 EARLY STUDY TERMINATION

The study can be terminated at any time at the discretion of the Sponsor. If the study is terminated prematurely, the Health Authorities will be notified per applicable guidelines. The Sponsor, or the Investigator will be responsible for informing IRBs and/or IECs of the early termination of the study, in accordance with local requirements.

The Investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patients' interests. In the event of early termination, patients should receive local standard of care at the physician's discretion. For patients who have received AUTO3, a long-term follow-up study for safety should continue under a separate protocol for up to 15 years post infusion as per Health Authority guidelines.

3.10 NUMBER OF PATIENTS

It is anticipated that approximately 171 patients will be enrolled (consented) into the study and approximately 151 patients receiving the treatment as outlined below:

- **Phase I:** A dose escalation and expansion cohort involving approximately 50 treated patients in total (up to 6 patients per dose cohort, dose level 1 may include up to 12 patients).

- **Phase II:** A Phase II involving up to a total of 101 patients; 81 with DLBCL subsets and transformed FL in Cohort 1, additionally, 20 patients with primary mediastinal large B cell lymphoma and those with lymphoma transformed from other indolent histologies in Cohort 2.

The sample size for Phase II of the study will follow Simon's 2-stage optimal design as described in Section .

4 SCIENTIFIC RATIONALE FOR STUDY

4.1 DESIGN RATIONALE

This single-arm dose-escalation Phase I/II study is designed to assess safety, tolerability, and optimum RP2D(s) and MTD, if an MTD exists, for AUTO3. Considering the experience the field has with targeting CD19 and CD22 individually, the novelty of targeting both CD19 and CD22 with a single construct expressing two CARs, as well as incorporation of consolidation or pre-conditioning treatment with an anti-PD-1 antibody (pembrolizumab), a cautious dose escalation design encompassing four dose levels is considered appropriate. A rolling 6 dose escalation design in the Phase I has been chosen, as it will facilitate dosing an adequate number of patients prior to evaluation of safety and biological activity, and to facilitate better decision making of the Phase II dose. In addition, considering that time required to manufacture individual products and the risk of rapid disease progress in these patients, a rolling 6 design is more optimal.

A dose escalation with ≤half log increase over the previous dose is appropriate considering the in-vivo expansion of the CAR T cells, other studies have used half-log/300% (Brudno and Kochenderfer 2016) to a log/1000% (Turtle et al. 2016) increase in dose. The proposed dose levels of 50×10^6, 150×10^6, 450×10^6 and 900×10^6 CD19/CD22 CAR-positive T cells are conservative and designed to identify a safe and efficacious dose or dose range for the Phase II. The rationale for starting dose levels and dosing schedule is outlined in detail in Sections 4.2 and 4.4.

Considering the first in human nature of the study, dosing an adequate number of patients at the starting dose without consolidation before initiating consolidation therapy is necessary and is incorporated into the design (Section 3.2). The rationale for pre-conditioning or consolidation with anti-PD-1 antibody (pembrolizumab) is further described in Section 4.6. The timing of initiation of anti-PD-1 consolidation therapy considers the time to peak expansion of the infused CAR T cells which is around 7 days (range 2 to 14 days) (Schuster et al. 2016), following which the number of circulating CAR T cells decreases over the next few weeks due to activation-induced cell death as well as exhaustion (Long et al. 2015). Additionally, CRS which occurs within the first week of T cell infusion in all patients (Schuster et al. 2014) is expected to have resolved in most patients by Day 14 (Lee et al. 2015). It is necessary to dose anti-PD-1 antibody before significant contraction of the CAR T cell compartment. Additionally, based on emerging data from the ZUMA-6 study involving axicabtagene ciloleucel in combination with atezolizumab which was administered starting on Day 1 (in addition to Day 21 and 14), no apparent exacerbation or recurrence of axicabtagene ciloleucel–related toxicity following atezolizumab infusion was observed (Jacobson et al. 2018). In another study with anti-CD19 CAR T therapy JCAR014 and the anti PD-L1 agent durvalumab, patients have been dosed with durvalumab one day prior to JCAR014 infusion. This combination and dosing regimen at escalating doses of durvalumab has been well tolerated to date (Hirayama et al. 2018). It is likely, based on the emerging safety profile of AUTO3 in this study and the AMELIA study (Amrolia et al. 2018), that early dosing of pembrolizumab is likely to be tolerable. Moreover, as PD-1 overexpression has been observed in CAR T cells, which possibly leads to exhaustion and hypofunction, early dosing of pembrolizumab on Day -1 may improve CAR T cell expansion, persistence, and functional killing. An additional reason for early dosing of pembrolizumab on Day -1 is to help CAR T cells engage tumour cells with de novo PD-L1 upregulation, which can be seen in 10% to 30% of patients with

DLBCL (Andorsky et al. 2011, Chen et al. 2013, Rossille et al. 2014, Kiyasu et al. 2015, Dong et al. 2016, Menter et al.)

The limited number of doses of anti-PD-1 antibody consolidation (three doses in total, given every 21 days) is considered adequate to facilitate induction of CRs which happen early with CAR T cell therapy, usually with in the first three months (Neelapu et al. 2016). This will also reduce the risk for any cumulative toxicity. An alternative approach, in which 1 dose of anti-PD-1 is administered during pre-conditioning, will be explored in Regimen B. Since most clinical responses occur in the first month and the maximal expansion and contraction of CAR T cells also happen during the same period, maintaining CAR T cell function over that period with a single dose of pembrolizumab may be adequate for optimal activity of the CAR T cells on the tumour. For these reasons we will explore Regimen B with a single dose of pembrolizumab on Day -1.

The option for delaying, withholding or withdrawing anti-PD-1 therapy based on emerging data is designed to add to safety.

During Phase I cell dose escalation, a minimum dosing interval of 2 weeks between patients is incorporated to reduce the risk of inducing severe adverse effects in more than one patient. During evaluation of alternative regimens of pembrolizumab at the same dose of CAR T cells, the inter-patient dosing interval of 7 days is considered adequate. Based on the totality of data from the current study, the study in paediatric ALL (Amelia study) (see Section 1.7), the risk of patients deteriorating during the inter-patient interval, and the safety of AUTO3 at previous dose levels and regimens, a 7-day inter-patient dosing interval is likely to be adequate. Additionally, close monitoring for up to 10 days after AUTO3 and up to 3 days after the first dose of anti-PD-1 therapy is designed to add to safety. A DLT assessment window of 28 days is incorporated and is appropriate as the therapy involves a single dose of AUTO3 and the majority of toxicities happen within the first few weeks (Davila et al. 2014). Considering the extensive clinical experience with these agents, this window is considered adequate even with the use of anti-PD-1 consolidation or pre-conditioning as it is unlikely to significantly increase AEs. Additionally, the DLT period will be extended to 2 weeks after the first dose of pembrolizumab in case the dosing of pembrolizumab is delayed and to capture any additive toxicity.

The rationale for Simon's 2 -stage optimal design for the Phase II (Cohort 1) part of the study is to allow for the termination of the study at interim analysis after 27 patients if the true response rate is 10% or less. The rationale for dosing up to 81 patients is to detect early signs of efficacy in addition to generating additional safety data at the RP2D(s).

4.2 POPULATION RATIONALE

AUTO3 is designed to specifically target CD19 and/or CD22, which are only expressed on normal and malignant B lymphocytes. The patient population for this study is DLBCL and large B-cell lymphoma subsets, and will include:

- DLBCL, not otherwise specified (NOS), per World Health Organisation classification and DLBCL with MYC and BCL2 and/or BCL6 rearrangements (double/triple hit).
- Transformed DLBCL from FL.
- Transformed DLBCL from other indolent lymphomas (excluding Richter's transformation).

- High-grade B cell lymphoma with MYC expression (excluding Burkitt's lymphoma).
- Primary mediastinal large B cell lymphoma.

In addition, since this is an experimental therapy, the study patient population will be restricted to patients with chemotherapy-refractory disease, or relapse after at least two lines of therapy (including an anti-CD20 monoclonal antibody and an anthracycline cycle), or after ASCT, and have PET-positive disease (for efficacy assessment).

Patients with lymphoma and history of central nervous system (CNS) involvement may also be included in the study. Tisagenlecleucel is a CAR T cell product approved by the European Medicines Agency and the FDA for the treatment of relapsed/refractory DLBCL. Both the pivotal Phase II trial (Schuster et al. 2019) and the Phase Ib (PORTIA; (NCT03630159 2018)) study allowed prior history of CNS disease and only excluded patients with active disease. Lisocabtagene maraleucel, another CD19 CAR T cell product, is currently being studied in two trials involving DLBCL (NCT02631044 2015, NCT03484702 2018). Both trials allow patients with prior as well as active CNS disease. Data presented thus far from NCT02631044 show Grade 3/4 CRS at 1% and Grade 3/4 NT at 12% (Abramson et al. 2018). Additionally, data from studies with anti CD19 CAR T therapies in relapsed/refractory ALL show no increased risk of NT in patients with CNS involvement by malignancy (Talekar 2017, Zhang 2018) and in a Phase I AUTO3 paediatric B-ALL trial that allows patients with CNS involvement with disease there have been no reports of Grade 3/4 NT attributed to AUTO3 (see Section 1.7 (Amrolia et al. 2018). Finally, in the ongoing AUTO3 trial in DLBCL, there has been one case of Grade 3 NT that resolved (Ardeshna et al. 2018).

As outlined in Section 1.1, the prognosis for patients who relapse after ASCT, or fail initial salvage is particularly poor. In patients with DLBCL that has progressed after ASCT, median OS is <10 months (Vose et al. 1992, Nagle et al. 2013). The median OS of patients requiring third-line treatment is 4.4 months (Van Den Neste et al. 2016). The prognosis of patients with histological transformation and FL Grade 3B is also poor (Section 1.1). Also, for patients with primary mediastinal lymphoma, cure rates are low for those who relapse or progress (Dunleavy and Wilson 2015)(Zelenetz 2019)(Crump et al. 2017)(Mills et al. 1995, Villela et al. 2001, Telio et al. 2012, Hitz et al. 2015)(Coiffier et al. 2002, Feugier et al. 2005)(Telio et al. 2012, Hitz et al. 2015). These patients are appropriate candidates for clinical trials, and data from existing trials of second-generation CD19 CAR T cells therapies in similar patient populations have been very promising with approved products in these subtypes (Kochenderfer et al. 2015, Kochenderfer et al. 2016, Neelapu et al. 2016). Dual targeting of CD19 and CD22 followed by consolidation or pre-conditioning with anti-PD-1 therapy is likely to improve outcomes further.

4.3 STARTING DOSE RATIONALE

The primary consideration for selection of a starting dose for the proposed trial is the safety of the patient. Considerations for CAR T cell dosing are challenging. Chimeric antigen receptor T cells are a "living therapy" i.e. they can engraft within the study patient, they can expand and they have no half-life in the standard conception of the term (Ghorashian et al. 2015). Efficacy and toxicity appears related to the magnitude and kinetics of engraftment (Maude et al. 2014). A wide range of doses have been utilised in existing studies of CD19 CAR T cell therapy in leukaemia and lymphomas (5×10^5 to 1.7×10^7 CAR T cells/kg), with no clear correlation between cell dose administered and efficacy, reflecting the fact that infused CAR T cells can expand by several logs after transfer to a lymphodepleted host. Consequently, the correlation between CAR T cell dose and toxicity is much less clear than the correlation with standard

small molecule or protein-based therapeutics. The findings are obscured by differences in CAR design and CAR T cell production processes. A dose in the order of millions of CAR T cells/kg appears generally optimal.

Considering the incorporation of consolidation or pre-conditioning therapy with anti-PD-1 antibody in this lymphoma study, the proposed starting dose of 50×10^6 CD19/CD22 CAR-positive T cells (AUTO3) is appropriate. It is approximately a third of the dose of 2×10^6 CD19 (CD28z) CAR-positive T cells/kg considered to be the MTD in the National Institute of Health and Kite Pharma studies in B cell lymphomas (Neelapu et al. 2016). This is also significantly lower than the UPENN's CTL019, a CD19 (41BB-ζ) CAR dose, where a higher dose of up to 500×10^6 ($5.10 - 6.75 \times 10^6$ cells/kg) was considered tolerable and the RP2D (Maude et al. 2014).

Dual targeting of CD19 and CD22 is not anticipated to result in more activity or toxicity over a CD19 or a CD22 CAR alone for several reasons: firstly, CD22 is significantly less densely expressed than CD19 on lymphoma cell lines so the cumulative targetable antigen density will not be significantly increased (Lee et al. 2014, Shah et al. 2015). Secondly, little if any synergy is anticipated from signalling through both of the TNF-family receptor endodomains, as a signal through either OX40 or 41BB is likely to saturate the common signalling pathway. In the absence of a CD28 co-stimulatory domain, less rapid proliferation is expected. Furthermore, no increase in cytotoxicity is observed in vitro between CD19 and CD19/CD22 CAR constructs with CD19-positive/CD22-positive target cells (IB Section 4.4.3). Only in situations where the targets lose expression of CD19 do we expect continued cytotoxicity with the CD19/CD22 CAR.

The proposed dose is lower than the starting doses of AUTO3 in paediatric ALL (1×10^6 CAR T cells/kg or approx. 75×10^6 CAR T cells) and similar to that used in other recent CAR studies in lymphoma i.e. 50×10^6 CAR T cells with JCAR017, a CD19 (41BB-ζ) CAR (Abramson et al. 2016) and 0.66×10^6 CAR T cells/kg (approx. 50×10^6 CAR T cells in total) with HuCAR-19, a CD19 (CD28-ζ) CAR (Brudno et al. 2016). The treatment of the first three patients at the starting dose without consolidation will provide additional clarity to the safety profile of the starting dose. The rationale for consolidation or pre-conditioning therapy is further discussed in Section 4.6. Moreover, the available data indicates that incorporation of anti-PD-1 antibody is unlikely to significantly increase proliferation, cytokine production or toxicity (IB Section 4.6 and (Cherkassky et al. 2016). In the single patient treated with this combination, no substantial CAR T cell proliferation or cytokine production was noted and, other than fever, therapy was well tolerated (Chong et al. 2016) and resulted in clinically significant anti-tumour response. The use of limited number of doses in the consolidation approach or single dose in the pre-conditioning approach is also likely to limit any potential additive toxicity.

In summary, considering the experience the field has with targeting CD19 and CD22 individually, the novelty of targeting both CD19 and CD22 with a single construct expressing two CARs, as well as incorporation of consolidation or pre-conditioning treatment with an anti-PD-1 antibody (pembrolizumab), the proposed starting dose of 50×10^6 CD19/CD22 CAR-positive T cells is considered appropriate.

4.4 RATIONALE FOR DOSING SCHEDULE

CAR T cell therapies are generally administered once, undergo significant expansion *in vivo* upon contact with the target antigen expressed on tumour cells and, particularly where a

41BB-ζ co-stimulatory domain is incorporated in to the CAR, persist long-term in a proportion of patients (Maude et al. 2014). It is anticipated that AUTO3 will have similar expansion and persistence *in vivo* to the CD19 CAR-positive T cells utilised in the UPENN studies, rendering the need for re-dosing unnecessary (Schuster et al. 2016). On occasion, a re-treatment dose may be given if the patient meets the criteria for re-treatment (Section).

All patients will receive a single dose of AUTO3. Cytokine surge, especially IL-15, observed during post-conditioning chemotherapy with fludarabine and cyclophosphamide (FLU-CY) occurs in the first few days and returns to baseline around 10 days later (Rossi et al. 2015). It may be ideal to dose the CAR T cells early within this window, as IL-15 is necessary for CAR T cell expansion, engraftment, and resulting efficacy (Xu et al. 2014).

The timing rationale for consolidation and pre-conditioning with pembrolizumab is described in Section 4.1. The pembrolizumab dose of 200 mg for consolidation is based on the prescribed label dose for other solid tumours. The dosing frequency of every 3 weeks (Regimen A: Days 14, 35 and 56 [±3 days]) is also based on the prescribed label for solid tumours. The total number of doses is limited to only three doses (Regimen A), and the rationale is based on the hypothesis that CAR responses happen early and limited duration of anti-PD-1 is adequate to induce CRs, and thus further continuation of pembrolizumab is likely unnecessary. For Regimen B, we chose a single pembrolizumab dose of 200 mg to be given on Day -1 as part of the pre-conditioning regimen. The peak expansion and the peak anti-tumour effect of CAR T cells generally occur in the first 2 weeks (Neelapu et al. 2017, Schuster et al. 2019). We have also observed this in Study AUTO3-DB1 (Ardeshna et al. 2018). Cytokine production and PD-1 upregulation also generally occur 2 weeks post-CAR T cell infusion (Kochenderfer et al. 2015, Locke et al. 2017). In addition, the majority of clinical responses are achieved within the first month post-CAR T infusion (Neelapu et al. 2017, Schuster et al. 2019). All CRs were achieved in 1 month in AUTO3-DB1 (Ardeshna et al. 2018). Given that the half-life of pembrolizumab is 23 days, a single dose of pembrolizumab on Day -1 prior to CAR T infusion is likely sufficient to minimise both the exhaustion of CAR T cells during expansion and the immune escape effect of PD-L1. Moreover, based on data from other studies, it is less likely that there will be an additional safety concern for dosing at Day -1. In a study with JCAR014 (NCT02706405 2016), patients were dosed with durvalumab safely on Day -1 prior to JCAR014 therapy (Hirayama et al. 2018) followed by multiple additional doses. For these reasons as well as for patient convenience, we plan to explore Regimen B of single dose pembrolizumab on Day -1 instead of 3 doses of pembrolizumab (Regimen A).

After treatment with AUTO3, safety will be monitored closely (both in hospital and as an outpatient/ambulatory care setting), and efficacy will be assessed periodically as described in the Schedule of Assessments. The timing of assessments is designed to capture early signs of toxicity and efficacy.

4.5 FLUDARABINE AND CYCLOPHOSPHAMIDE

Pre-conditioning strategies that deplete host lymphocytes prior to adoptive transfer of tumour specific T-lymphocytes is thought to enhance treatment efficacy by eliminating regulatory T cells and increasing access of the transfused CAR T cells to activating cytokines (Klebanoff et al. 2005, Wrzesinski and Restifo 2005). Cyclophosphamide has an established history in lymphodepleting regimens used prior to adoptive cell immunotherapy (Sporn et al. 1993, Curti et al. 1998, Brentjens et al. 2011, Chu et al. 2012). It is used alone or often used in combination with other agents (Dudley et al. 2008, Laurent et al. 2010, Geller et al. 2011) such as FLU

(Louis et al. 2011). The FLU-CY combination is well tolerated in chronic lymphocytic leukaemia (Hallek 2013).

Cyclophosphamide and FLU based pre-conditioning have become the preferred regimen for CAR T therapies and have been used in multiple studies (Lee et al. 2014, Kochenderfer et al. 2015, Ali et al. 2016). In terms of overall efficacy, the FLU-CY combination is also considered to be superior to CY alone (Lee et al. 2016, Turtle et al. 2016).

The exact dose regimens used for lymphodepletion prior to CAR T cell therapy are variable (IB Section 7.2). The regimen utilised in this study (FLU 30 mg/m^2/day for 4 days + CY 500 mg/m^2/day for 2 days) is similar to that evaluated in multiple clinical studies across institutions and appears both safe and active (Lee et al. 2014, Ali et al. 2016, Fry 2016, Kochenderfer et al. 2016, Neelapu et al. 2016, Turtle et al. 2016). See Section 7.2 of the IB for further background information relating to the pre-conditioning treatment.

In the current study, we propose to start at a low dose of 50 × 10^6 CD19/CD22 CAR-positive T cells combined with low dose FLU-CY (FLU 30 mg/m^2/day for 4 days and CY 500 mg/m^2/day for 2 days) based pre-conditioning regimen and titrate the CAR T dose up based on emerging safety data. A 3-day washout period prior to infusion of AUTO3 is also incorporated, taking into consideration the 20-hour half-life of FLU. FLU and CY will both start on Day -6. We also propose to include pembrolizumab 200 mg × 1 dose at Day -1 as part of pre-conditioning as this will be done prior to AUTO3 infusion (Regimen B).

In summary, given the nature of the patient population and the role of FLU-CY and pembrolizumab in enhancing the clinical efficacy of CAR T cells, the proposed dose and regimen is justified.

4.6 ANTI-PD-1 CONSOLIDATION / PRE-CONDITIONING RATIONALE

As described in Section 1.4 and in Section 7.7 of the IB, increases in PD-L1 expression by tumour cells is a crucial part of the tumour's adaptive resistance to T cell mediated immune response including adoptively transferred engineered T cells.

In addition, early CAR T cell exhaustion can potentially limit the effectiveness of the therapy and pre-clinical data suggest CAR T cell function can be restored by using an anti-PD-1 antibody (Section 1.4). Similarly, we have observed that CD19/22 CAR T cells become exhausted after repeated stimulation. Our pre-clinical data also show that repeated antigen stimulation leads to PD-1 as well as PD-L1 overexpression on CD19/CD22 CAR T cells. These cells generate fewer cytokines compared with fresh unstimulated CD19/CD22 CAR T cells and induce less cytotoxicity when compared with fresh CD19/CD22 CAR T cells in PD-L1 expressing tumours, suggesting exhaustion. The addition of anti-PD-1 antibody restored both AUTO3 cytokine production and cytotoxicity in DLBCL in *in vitro* systems.

Clinically, pembrolizumab and other PD-1/PD-L1 inhibitors have also been used to improve CAR T cell function. Several Investigators have added PD-1 or PD-L1 inhibitors to CAR T cells in order to mitigate the effect of exhaustion and to enhance expansion, persistence, or restore tumour killing. Maude et al showed that all 4 patients with B ALL who progressed after tisagenlecleucel treatment, demonstrated re-expansion of CAR T cells following pembrolizumab treatment (Maude et al. 2017). This translated into objective responses in 4 patients with extramedullary relapse and re-establishment of B cell aplasia in 3/6 patients (Li et al. 2018). Chong et al observed a re-expansion of CD19 CAR T cells with pembrolizumab in 8/11 patients with DLBCL who progressed after tisagenlecleucel administration (Chong et

al. 2018). This translated into an ORR of 25%. Jacobson et al showed that addition of atezolizumab to axicabtagene ciloleucel led to a doubling of CAR T cell expansion, measured by the area under the curve (AUC) compared to patients treated with axicabtagene ciloleucel alone (Jacobson et al. 2018). In this study, relapsed or refractory DLBCL patients were administered atezolizumab every 21 days for 4 doses starting on Day 21, 14, or on 1 post-axicabtagene ciloleucel infusion. Severe toxicity such as Grade ≥3 CRS and neurologic events occurred in 3 (25%) and 6 (50%) patients, respectively. This was not significantly different from that seen with axicabtagene ciloleucel alone in the ZUMA-1 study, despite >2-fold higher AUC in ZUMA-6 than the median observed in patients treated with axicabtagene ciloleucel alone in ZUMA-1. In another study in similar patients with relapsed/refractory B cell lymphomas, the PD-L1 inhibitor durvalumab was dosed at Day -1 prior to JCAR014 (NCT02706405 2016). Up to 10 doses of durvalumab were administered at 4-week intervals until toxicity or disease progression. CRS and NT were seen in 38% and 8% of patients, respectively. The early results indicate that Day -1 dosing of durvalumab prior to JCAR014 appears to be safe (Hirayama et al. 2018).

The data from AUTO3 in DLBCL, when combined with 3 doses of pembrolizumab, also have not shown any Grade 2 or higher CRS and no neurotoxicities have been reported in patients treated with AUTO3 and pembrolizumab. These data provide evidence to support the safe combination of pembrolizumab with CAR T cells with no additive toxicity, severe CRS or NT in relapsed refractory DLBCL patients. In our preliminary Phase I data, at the lowest dose level of 50×10^6 CD19/22 CAR-positive T cells, where 4 patients did not receive pembrolizumab and 3 patients received pembrolizumab 14 to 21 days after AUTO3 infusion, we observed that the only patients who received pembrolizumab had persistent CAR T cells at 2 months. None of the patients who did not receive pembrolizumab had persistence of CAR T cells at 2 months. It is likely that early dosing of pembrolizumab will further reduce CAR T cell exhaustion.

These data suggest that the addition of pembrolizumab to CAR T cell therapy is likely to be tolerable and unlikely to significantly worsen the safety profile of AUTO3. Moreover, considering the pre-clinical data, the timing and kinetics of CAR T cell expansion and contraction in patients (median time to peak is 14 days), dosing with pembrolizumab on Day -1 prior to AUTO3 infusion should be explored. This would also allow pembrolizumab to engage with tumour cells expressing de novo PD-L1 in addition to prevent early exhaustion and improve overall expansion and engraftment of CAR T cells. This is likely to complement the impact of FLU-CY pre-conditioning, which induces an IL-7 and IL-15 surge to increase CAR T cell engraftment and expansion.

For safety reasons, pembrolizumab will be first introduced after peak expansion of CAR T cells and should that regimen (Regimen A - consolidation) be safe, then it will be given prior to CAR T cell infusion (Regimen B - pre-conditioning) to optimise the impact of pembrolizumab on CAR T cell exhaustion.

Based on the rationale described above in Section 1.4 and considering the low starting dose and cautious study design, the proposed incorporation of limited duration (3 doses, Section 4.4) anti-PD-1 (pembrolizumab) consolidation or pre-conditioning is justified.

4.7 BIOMARKER COLLECTION AND ASSESSMENT RATIONALE

Current experience with CAR T cell therapies indicate that the safety depends on the disease burden, CAR T proliferation, and cytokine release, and efficacy depends on CAR T proliferation and persistence. To this end, the current biomarker strategy is designed to assess

blood cytokine levels and CAR T levels and persistence at various time points after AUTO3 infusion. In addition, BM sampling will be performed to assess disease status and expression of CD19/CD22 CAR Tpositive cells, which will help evaluate efficacy as well as resistance Additional optional samples may be collected to assess CY and/or FLU drug levels.

5 RISKS AND MITIGATION STRATEGY

This exploratory study is designed to assess the safety and biological activity of different doses of AUTO3 in a limited number of patients. Given the treatment novelty, this study will involve patients whose disease has progressed after treatment with the main approved classes of agents. Such patients are considered to have poor prognosis and are candidates for promising experimental therapies.

5.1 LEUKAPHERESIS

This is necessary for enrolling onto this study, as it is a prerequisite for preparing AUTO3. Cell production efficiency of at least 80% is anticipated and is dependent on the quality of the leukapheresate. AUTO3 infusion may or may not provide clinical benefit to these patients. Risks of leukapheresis are summarised in Table 9.

Table 9: Leukapheresis – Risks and Mitigation Strategy

Risks	Mitigation Strategy
Pain and bruising due to insertion of cannula/ central venous access.	Experienced clinicians/nurses performing the procedure, analgesics to be used as needed for pain.
Bacterial bloodstream infections associated with the insertion of access and return venous access devices.	The procedure will be carried out by trained and experienced personnel and risks will be minimised by strict adherence to aseptic measure.
Symptoms of hypocalcaemia e.g. muscle cramps due to chelation by anticoagulants used to prevent clotting.	Patients will be monitored for symptoms of hypocalcaemia, the rate of citrate infusion to the patient and duration of the procedure will be controlled by experienced personnel. Calcium supplements will be given as needed.

5.2 FLU-CY PRE-CONDITIONING CHEMOTHERAPY

Pre-conditioning with CY and FLU will only be undertaken after confirmation of the successful production of AUTO3. The risks of pre-conditioning with chemotherapy are summarised in Table 10. Please refer to the Summary of Product Characteristics (SmPC) or United States Prescribing Information (USPI) for more details.

Table 10: Pre-conditioning Chemotherapy – Risks and Mitigation Strategy

Risks	Mitigation Strategy
Myelosuppression resulting in anaemia, thrombocytopenia, and lymphopenia, are the most common toxicities. Moderate to severe myelosuppression is possible. Nadir for granulocyte is 1 to 2 weeks and platelets 2 to 4 weeks after chemotherapy, with recovery usually within 4 to 6 weeks. Neutropenic fever, infections, sepsis, and septic shock may occur and may sometimes be fatal.	The FLU and CY chemotherapy given is milder compared to general chemotherapy received by patients and will be given only once (one cycle, given over 4 days). Anti-microbial prophylaxis (including pneumocystis prophylaxis and acyclovir) may be given to prevent infections and if infections arise, these will be treated as per institutional guidelines. Blood, platelet and fresh frozen plasma transfusions will be given as per standard institutional guidelines. All sites have extensive expertise in managing these complications.
Cyclophosphamide associated toxicities including, but not limited to haemorrhagic cystitis, pyelitis, myocarditis and myo-pericarditis, pneumonitis and pulmonary fibrosis; veno-occlusive liver disease (per approved label) may also occur.	Given the low dose and short duration of treatment, these toxicities are unlikely. Patients will be given anti-emetic prophylaxis and hydration during lymphodepletion as per institutional policy. If haemorrhagic cystitis occurs, i.v. fluids and mesna will be given. Other toxicities will be managed as per standard institutional policy and by trained personnel.
Fludarabine is generally well tolerated: the most common side effects are lymphopenia and infection. Serious and sometimes fatal infections, including opportunistic infections and reactivations of latent viral infections such as Herpes zoster, Epstein-Barr virus, and progressive multifocal leukoencephalopathy, have been reported in patients treated with higher doses and for much longer durations. Neurotoxicity can occur but generally at higher doses. Other associated toxicities (as per the label) include but are not limited to autoimmune disorders, hepatic impairment, neuro-toxicity, and renal impairment.	Given the low dose and short duration of treatment, these toxicities are less likely to occur. Toxicities will be managed as per standard institutional policy and by trained personnel.

CY=cyclophosphamide; FLU=fludarabine; i.v.=intravenous

5.3 AUTO3 INFUSION

Risks associated with the infusion of AUTO3 are presented in Table 11.

Table 11: AUTO3 Infusion – Risks and Mitigation Strategy

Risks	Mitigation Strategy
Infusion reactions may occur with the infusion of AUTO3.	The product is autologous and the risk is likely to be low. Patients will be pre-medicated with diphenhydramine/chlorpheniramine and paracetamol/acetaminophen (Section 10.3).
Cytokine-release syndrome is a recognised toxicity associated with CAR T cell therapies. Clinical symptoms indicative of CRS includes culture negative fever, but may also include myalgia, nausea/vomiting, tachycardia, hypoxia, hypotension, headache, confusion, tremor, and delirium. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure, and	Patients will be monitored for CRS and appropriate treatment will be given in the event of the occurrence (Section 10.4).

Risks	Mitigation Strategy
disseminated intravascular coagulation (DIC). The clinical features may overlap with macrophage activation syndrome.	
Neurotoxicity has been seen in patients with lymphoma after treatment with CAR T cell therapy and is now referred to as ICANS. The cause of NT is not well-understood, although it is generally reported to be fully reversible. Although symptoms can vary, the early manifestations of ICANS are often tremor, dysgraphia, mild difficulty with expressive speech especially naming objects, impaired attention, apraxia, and mild lethargy. Other symptoms can include confusion, depressed level of consciousness/encephalopathy, hallucinations, dysphasia, ataxia, apraxia, cranial nerve palsies, and seizures. Headache is a non-specific symptom, frequently occurring during fever or after chemotherapy; thus, headache alone is not a useful marker of ICANS. Expressive aphasia, on the other hand, appears to be a very specific symptom of ICANS.	The patient will be closely monitored for neurological signs and symptoms, and neuroimaging will be performed as appropriate. Appropriate treatment, including dexamethasone, will be provided in the event of severe NT, including cerebral oedema and seizures (Section 10.6).
Cytopenia (neutropenia, thrombocytopenia and anaemia) has been seen in patients with leukaemia and lymphoma after treatment with CAR T cell therapy, though is often confounded by the patient's prior treatments, disease state at the time of treatment and the pre AUTO3 lymphodepletion chemotherapy. The cytopenia may be prolonged but resolves in most individuals (Locke et al. 2019).	Patients should be supported according to local institutional practice. Patients with low neutrophil counts will receive prophylactic antibiotics and antiviral medications if clinically appropriate and in accordance with local practice. All patients with fevers and neutropenia will have blood cultures drawn and broad-spectrum antibiotic coverage initiated promptly.
Off-tumour toxicity could be due to either on-target (due to expression of the antigen on non-tumour cells) or off-target (recognition of a molecular target other than CD19 or CD22) interactions. Historically, there have been reports of on-target/off-tumour toxicity with CAR therapy as well as T cell receptor engineered T cells; the details are described in the IB.	Pre-clinical toxicology indicates the risk to be low as CD19 and CD22 expression is largely limited to the B cell lineage. Ongoing CD19 and or CD22 CAR studies have not shown significant off-target toxicity. Considering the body of knowledge concerning targeting CD19 and CD22, this risk is likely to be low.
Tumour lysis syndrome (TLS) may occur on treatment with AUTO3 due to rapid destruction of malignant cells in the context of a high tumour burden, although this is rarely seen after CD19 CAR-positive T cell therapy in lymphoma.	If TLS occurs, all sites have extensive experience in managing this complication and supportive care will be initiated rapidly as per standard institutional protocols. (See Section 10.7).
Hypogammaglobulinaemia may occur because of depletion of normal B cells by AUTO3. Potentially this may increase the risk of infections. The degree of hypogammaglobulinaemia and its duration are variable depending on the persistence of CAR T cells.	B cell recovery and Ig levels will be monitored regularly following AUTO3 infusion. Patients with recurrent infections and persistent, severe hypogammaglobulinaemia will receive i.v. Ig replacement (Section 10.8).
Sepsis: Sepsis leading to death has been noted in three patients treated with very high doses (5×10^8 CAR T cells) of CD19 CAR in a study done at UPENN.	Gradual titration of dose, prophylactic antibiotics and antiviral medications, close monitoring of patients and early intervention is likely to reduce the risk.
Insertional mutagenesis: Disruption of the cellular transcriptome by retroviral-mediated insertional mutagenesis has, in rare cases and in haematopoietic stem cell gene therapy trials, given rise to haematopoietic stem	T cells that have been transduced with a retrovirus have, to date, been proven safe. Unlike haematopoietic stem cells, T cells are highly resistant to retroviral vector-induced

Risks	Mitigation Strategy
cells with elevated expression of growth-related genes, which subsequently resulted in T cell leukaemia and/or lymphoma.	transformation. The patients will be monitored for secondary malignancy and survival in a long-term follow-up protocol for up to 15 years following treatment with AUTO3 (see Section 8.7).
Risks associated with a replication competent retrovirus (RCR): There is a risk that a recombination event may occur during vector production that results in an RCR, which may be pathogenic in humans.	All vector lots are tested for RCR prior to release to sites. The risks of an RCR are unknown. To date, no patient has developed an RCR with a retroviral based CAR T cell therapy. Patients will be monitored for RCR by polymerase chain reaction (PCR) during their scheduled follow-up visits. If a positive signal is confirmed, additional testing will be performed and medical and research experts will be consulted for the optimal treatment approach should any complication arise.
Immunogenicity	Evaluations to assess immunogenicity will be performed in this study. Anti-CAR antibodies or anti-CAR T cell response could be neutralising; reduced efficacy is possible in patients who develop them due to either neutralisation or enhanced clearance (Section 9.3.4)
Dimethyl sulfoxide (DMSO), which is part of cryopreservative buffer, may cause an abnormal taste at the time of infusion and body odour lasting 1 to 2 days afterwards. At high doses, DMSO may cause nausea, vomiting, abdominal pain, headache, and haemolysis. Rarely, patients may experience mild or severe cardiac, pulmonary, renal, or neurological symptoms.	Most patients are likely to be exposed to a small dose of DMSO; even at the highest dose, the median amount of DMSO exposure is likely to be 13 g and maximum 26 g, which is significantly lower than the general institutional maximum limit of 70 g. Additionally, at these dose levels, the side effects are likely to be mild and short lasting.
Safety oversight of the patients dosed with AUTO3 in an outpatient/ambulatory care setting: After CAR T cells infusion, patients require monitoring while they are at risk for the development of CRS or ICANS.	The sites selected have experience with either outpatient CAR T administration and/or outpatient stem cell transplantation to ensure adequate management follow-up of patients dosed with AUTO3. In addition, toxicities will be managed as per standard institutional policy and by trained personnel. Exclusion criteria have also been implemented specifically for the outpatient cohort.

ALL=acute lymphoblastic leukaemia; CAR=chimeric antigen receptor; CD19=cluster of differentiation 19; CD22=cluster of differentiation 22; CRS=cytokine release syndrome; DIC=disseminated intravascular coagulation; DMSO=dimethyl sulfoxide; ECHO=echocardiogram; g=gram; IB=Investigator's Brochure; ICANS=immune effector cell-associated neurotoxicity syndrome; Ig=immunoglobulin; i.v.=intravenous; MUGA=multigated acquisition; PCR=polymerase chain reaction; RCR=replication competent retrovirus; TLS=tumour lysis syndrome; UPENN=University of Pennsylvania.

5.4 ANTI-PD-1 (PEMBROLIZUMAB) (PRE-CONDITIONING or CONSOLIDATION) THERAPY

Administration of anti-PD-1 antibody during pre-conditioning or after CD19/CD22 CAR-positive T cells (AUTO3) is thought to prevent tumour cell escape due to upregulation of PD-L1. The consolidation therapy regimen starting after AUTO3 administration will be undertaken after any CRS and NT have resolved. The risks associated with anti-PD-1

(pembrolizumab) are presented in Table 12. Please refer to the SmPC or USPI for more details. Use of a single dose of pembrolizumab as part of a modified pre-conditioning regimen may have a lower risk of immune toxicity.

Table 12: Anti-PD-1 AUTO3 Consolidation or Pre-conditioning Therapy – Risks and Mitigation Strategy (per SmPC)

Risks	Mitigation Strategy
Immune-mediated pneumonitis, including death	Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a taper) for Grade 2 or greater pneumonitis. Withhold pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue pembrolizumab for severe (Grade 3) and life-threatening (Grade 4) pneumonitis.
Immune-mediated colitis	Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold pembrolizumab for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue pembrolizumab for life-threatening (Grade 4) colitis.
Immune-mediated hepatitis	Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.
Immune-mediated endocrinopathies including, hypophysitis, thyroid disorders and Type 1 diabetes mellitus	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold pembrolizumab for moderate (Grade 2) hypophysitis and withhold or discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) hypophysitis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thioamide and beta-blockers as appropriate. Withhold or discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism Monitor patients for hyperglycaemia or other signs and symptoms of diabetes. Administer insulin for Type 1 diabetes; withhold pembrolizumab and administer an anti-hyperglycaemic in patients with severe hyperglycaemia.
Immune-mediated nephritis and renal dysfunction	Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold pembrolizumab for moderate (Grade 2), and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) nephritis.
Other immune-mediated adverse reactions	For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids

Risks	Mitigation Strategy
Infusion-related reactions: pembrolizumab can cause severe or life-threatening infusion-related reactions, which have been reported in 0.2% of patients receiving pembrolizumab	Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue pembrolizumab.
Embryo-foetal toxicity, based on its mechanism of action, pembrolizumab can cause foetal harm when administered to a pregnant woman	Advise females of reproductive potential to use highly effective contraception during treatment with pembrolizumab and for 4 months after the last dose of pembrolizumab (or 12 months after AUTO3 whichever is longer).

5.5 UNKNOWN LONG-TERM RISKS OF GENE THERAPY

Following completion of this study, all patients will be invited to enrol in a long-term follow-up study and monitored for up to 15 years for AUTO3 treatment-related SAEs, AEs of interest, including new secondary malignancies, and survival.

6 PATIENT POPULATION

Patients will be eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies. There will be no exception to the eligibility requirements at the time of registration. Ensuring patient eligibility is the responsibility of the Principal Investigator or other delegated Investigator(s).

6.1 INCLUSION CRITERIA

Patients must meet all the following criteria for study entry:

1. Male or female, aged ≥18 years.
2. Willing and able to give written, informed consent to the current study.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1.
4. Histologically confirmed DLBCL and large B cell lymphoma subsets, including:

   Phase I and Phase II Cohort 1:

   a. DLBCL, not otherwise specified (NOS), per World Health Organisation classification and DLBCL with MYC and BCL2 and/or BCL6 rearrangements (double/triple hit).

   b. Transformed DLBCL from FL. High-grade B cell lymphoma with MYC expression (excluding Burkitt's lymphoma).

   Phase I and Phase II Cohort 2:

   c. Transformed DLBCL from other indolent lymphomas (excluding Richter's transformation).
5. Chemotherapy-refractory disease, defined as one or more of the following:

   a. Stable disease (duration of stable disease must be less than or equal to 12 months) or progressive disease as best response to most recent chemotherapy containing regimen. Refractory disease after frontline chemo-immunotherapy is allowed.

   b. Disease progression or recurrence in ≤12 months of prior ASCT.**OR**
6. Relapse after at least two lines of therapy or after ASCT. At a minimum:

   a. Patients must have received rituximab or another anti-CD20 monoclonal antibody (unless Investigator determines that tumour is CD20-negative) and an anthracycline-containing chemotherapy regimen.

   b. Patients must have either failed ASCT, or be ineligible for or not consenting to ASCT.

   c. Patients with transformed DLBCL must have received at least one line of therapy after transformation to DLBCL.
7. PET-positive disease per Lugano classification.
8. For females of childbearing potential (defined as <24 months after last menstruation or not surgically sterile), a negative serum or urine pregnancy test must be documented at screening, prior to pre-conditioning and confirmed before receiving the first dose of study treatment.
   For females who are not postmenopausal (<24 months of amenorrhea) or who are not surgically sterile (absence of ovaries and/or uterus), two methods of contraception

comprising of one highly effective method of contraception together with a barrier method must be used during the treatment period and for at least 12 months after the last dose of study treatment. They must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 12 months after receiving the last dose of study drug (please refer to Appendix 3).

9. For males, it must be agreed that two acceptable methods of contraception are used (one by the patient – usually a barrier method, and one highly effective method by the patient's partner as defined in Appendix 3) during the treatment period and for at least 12 months after the last dose of study treatment and that sperm will not be donated during the treatment period and for at least 12 months after the last dose of study treatment.
10. Adequate renal, hepatic, pulmonary, and cardiac function defined as:
    a. Creatinine clearance ≥40 cc/min.
    b. Serum alanine aminotransferase/aspartate aminotransferase ≤2.5 × upper limit of normal (ULN).
    c. Total bilirubin ≤1.5 × ULN, except in patients with Gilbert's syndrome.
    d. LVEF ≥50% (by echocardiogram [ECHO] or multigated acquisition scan [MUGA]) unless the institutional lower limit of normal is lower.
    e. Baseline oxygen saturation >92% on room air and ≤Grade 1 dyspnoea.
11. Patient has adequate BM function without requiring ongoing blood product or granulocyte-colony stimulating factor support and meets the following criteria:
    a. Absolute neutrophil count ≥1.0 × 10^9/L.
    b. Absolute lymphocyte count ≥0.3 × 10^9/L (at enrolment and prior to leukapheresis).
    c. Haemoglobin ≥80 g/L.
    d. Platelets ≥75 × 10^9/L.
12. No contra-indications for leukapheresis.

6.2 EXCLUSION CRITERIA

Patients meeting any of the following exclusion criteria must not be enrolled into the study:

1. Prior allogeneic haematopoietic stem cell transplant.
2. Females who are pregnant or lactating.
3. History or presence of clinically relevant CNS pathology such as epilepsy, paresis, aphasia, stroke within 3 months prior to enrolment, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, uncontrolled mental illness, or psychosis.
4. Patients with active CNS involvement by malignancy. Patients with history of CNS involvement with malignancy may be eligible if CNS disease has been effectively treated and provided treatment was at least 4 weeks prior to enrolment (at least 8 weeks prior to AUTO3 infusion).

5. Clinically significant, uncontrolled heart disease (New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, sick-sinus syndrome, or electrocardiographic evidence of acute ischaemia or Grade 3 conduction system abnormalities unless the patient has a pacemaker) or a recent (within 12 months) cardiac event.
    - Uncontrolled cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded).
    - Evidence of pericardial effusion.
6 Patients with a history (within 3 months) or evidence of pulmonary embolism requiring ongoing therapeutic anticoagulation at the time of pre-conditioning.
7 Patients with active gastrointestinal (GI) bleeding.
8 Patients with any major surgical intervention in the last 3 months.
9 Active bacterial, viral or fungal infection requiring systemic treatment. Active or latent hepatitis B infection or hepatitis C infection. Testing positive for human immunodeficiency virus, human T cell lymphotropic virus (HTLV1 and 2) or syphilis.
10. History of autoimmune disease (e.g. Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 24 months.
11. Patients with a known history or prior diagnosis of optic neuritis or other immunologic or inflammatory disease affecting the CNS.
12. Evidence of active pneumonitis on chest computed tomography (CT) scan at screening or history of drug-induced pneumonitis, idiopathic pulmonary fibrosis, organising pneumonia (e.g. bronchiolitis obliterans), or idiopathic pneumonitis. Prior radiation pneumonitis in the radiation field (fibrosis) is allowed (if >24 weeks since the event).
13. History of other malignant neoplasms unless disease free for at least 24 months (carcinoma *in situ*, non-melanoma skin cancer, breast or prostate cancer on hormonal therapy allowed).
14. Prior treatment with PD-1, PD-L1, or cytotoxic T lymphocyte-associated protein 4 targeted therapy, or TNF receptor superfamily agonists including CD134 (OX40), CD27, CD137 (41BB), and CD357 (glucocorticoid-induced TNF receptor family-related protein) within 6 weeks prior to AUTO3 infusion (excluding study treatment with pembrolizumab on Day -1).
15. Prior treatment with investigational or approved gene therapy or cell therapy products until a dose level has treated at least three patients and has been declared safe.
16. Prior CD19 or CD22 targeted therapy.
17. The following medications are excluded:
    - Steroids: Therapeutic doses of corticosteroids within 7 days of leukapheresis or 72 hours prior to AUTO3 administration. However, physiological replacement, topical, and inhaled steroids are permitted.
    - Immunosuppression: Immunosuppressive medication must be stopped ≥2 weeks prior to leukapheresis or AUTO3 infusion.

- Cytotoxic chemotherapies within 2 weeks of AUTO3 infusion and 1 week prior to leukapheresis (2 weeks for lymphodepleting chemotherapy).
- Antibody therapy use including anti-CD20 therapy within 2 weeks prior to AUTO3 infusion, or 5 half-lives of the respective antibody, whichever is shorter.
- Granulocyte-colony stimulating factor less than 10 days prior to leukapheresis. Live vaccine ≤4 weeks prior to enrolment.
- Prophylactic intrathecal therapy: Methotrexate within 4 weeks and other intrathecal chemotherapy (e.g. Ara-C) within 2 weeks prior to starting pre-conditioning chemotherapy.

18. Prior limited radiation therapy (e.g. radiation to bone metastasis for pain control) within 4 weeks of AUTO3 infusion or chest/mediastinal radiation within 24 weeks of AUTO3 infusion.
19. Research participants receiving any other investigational agents, or concurrent biological, chemotherapy, or radiation therapy.
20. Known allergy to albumin, dimethyl sulphoxide (DMSO), CY or FLU, pembrolizumab or tocilizumab.
21. Any contraindications to receive anti-PD-1 antibody pembrolizumab will be excluded from cohorts requiring administration of pembrolizumab.
22. Patients, who in the opinion of the Investigator, may not be able to understand or comply with the safety monitoring requirements of the study.
23. Any other condition that in the Investigator's opinion would make the patient unsuitable for the clinical trial.

Phase I Expansion Cohort:

24. Subjects who do not have caregiver support (in line with institutional outpatient transplant guidelines) for outpatient/ambulatory care setting.
25. Subjects who are staying greater than 60 minutes (or whatever is permissible per institutional outpatient transplant guidelines) from the clinical trial site at the time of treatment.

PATIENT ELIGIBILITY TO RECEIVE AUTO3: Patients meeting any of the following criteria must not initiate pre-conditioning or infusion with AUTO3 (or pembrolizumab on Day -1) or must have the AUTO3 infusion delayed until they no longer meet these criteria:

1. Severe intercurrent infection.
2. Requirement for supplementary oxygen or active pulmonary infiltrates.
3. Clinical deterioration of organ function (renal and hepatic) exceeding the criteria set at study entry.

7 ATIMP: AUTO3

7.1 AUTO3 DESCRIPTION

AUTO3 is an ATIMP consisting of autologous enriched T cells retrovirally transduced to express two CARs, targeting CD19 and CD22, both on the same cell. AUTO3 also contains non-transduced autologous lymphocytes as a product-related impurity.

AUTO3 is presented in a CryoMACS® bag as a suspension in saline/human albumin solution/DMSO. The final product, AUTO3, may consist of one or more CryoMACS® bags for i.v. infusion.

7.2 AUTO3 MANUFACTURING

The Sponsor is responsible for the manufacturing of the drug product, AUTO3, according to Good Manufacturing Practice (GMP) principles and guidelines applicable to ATIMPs. The starting material for generation of AUTO3 is an unstimulated leukapheresate from the patient, which will be performed at the study site apheresis collection unit. This may require insertion of central venous access and is a day case procedure to collect peripheral blood mononuclear cells (PBMCs) only. Sites will be responsible for ensuring that the patient biological screening and leukapheresis procedures, including the labelling and issue of the leukapheresis product are carried out per the Human Tissue (Quality and Safety for Human Application) Regulations (SI 2007/1523) and in line with local procedures.

The leukapheresis procedure will be performed by the apheresis unit staff as described in Section 8.2. The collected PBMCs will be transported to the Sponsor Manufacturing Unit for generation of AUTO3, under aseptic GMP conditions. Further details regarding this process can be found in the Investigational Medicinal Product Dossier (IMPD) or in Module 3 of the Investigational New Drug (IND).

AUTO3 will be generated by *ex vivo* transduction of activated PBMCs using an engineered murine leukaemia virus-derived retroviral vector [redacted] containing the CD19/CD22 CAR expression cassette. The retroviral vector is produced under GMP conditions by [redacted] cotransfection of HEK293T cells and subsequent harvest and purification of the culture supernatant. In brief, cells from the leukapheresate are washed and activated with mitogenic ligands and cytokines. After activation, cells are transduced in bags with the retroviral vector. Post-transduction, cells are expanded for between 3 and 6 days to produce adequate dose. The appropriate dose of cells is then transferred to a CryoMACS® bag and formulated with a saline/human albumin solution/DMSO buffer. Full release testing will be performed to pre-defined specifications. AUTO3 manufacture and release will take approximately 4 weeks. AUTO3 will be cryopreserved in a sealed CryoMACS® bag and stored in a vapour-phase liquid nitrogen environment prior to administration. Further details regarding this process can be found in the IMPD or in Module 3 of the IND. All AUTO3 products will be released by a Qualified Person (QP) (see also Section).

Please refer to the AUTO3 IB, IMPD or in Module 3 of the IND, and CHM for further details on the manufacture of AUTO3, shipment, storage, and handling.

7.3 PACKAGING AND LABELLING

AUTO3 is supplied as a cryopreserved cell suspension in a sealed CryoMACS® bag containing the required number of CD19/CD22-CAR-positive T cells for the planned dose level. Each

AUTO3 CryoMACS® freezing bag will be labelled and will include all the required information, including the exact cell content, as applicable per local regulations.

CryoMACS® freezing bags are single use, sterile, containers intended for a single cycle of freezing, storage (down to -196°C), and subsequent thawing (at 37°C) of AUTO3 cells. The CryoMACS® freezing bags are comprised of a freezing bag (with access ports) as the primary containment for AUTO3 and an overwrap bag as secondary containment. Additionally, the CryoMACS® freezing bag has a built-in label pocket, which allows for the insertion of the patient label to include patient identification and product specifications for AUTO3. As part of the bag assembly, two spike ports are available which allow access to the bag contents for therapeutic use of the product (via attachment of a sterile transfusion assembly).

All AUTO3 products supplied will be released by a QP in line with national and/or EU requirements.

7.4 SUPPLY AND STORAGE

Cryopreserved AUTO3 will be supplied to the study sites (authorised to receive genetically modified organisms, in accordance with local requirements) by the Sponsor. Transport of AUTO3 to the study site will be performed in validated shippers under controlled temperature conditions below -150°C. In the case of a temperature excursion occurring during transit, the disposition of AUTO3 will be decided following the review of the temperature data by the responsible QP or their designee. All temperature excursions outside the storage conditions specified in the IMPD/Module 3 of the IND/Labels/Trial-Specific Procedures for receipt and storage of AUTO3 must be documented and reported to the Sponsor via the Clinical Research Associate as per the CHM. The Sponsor must be informed immediately if a patient has been administered AUTO3 where a temperature excursion has occurred.

The Investigator/pharmacist/designated personnel will take an inventory and acknowledge receipt of all shipments of the study product to confirm the shipment condition and content.

AUTO3 must be stored at below -150°C, under controlled temperature and alarmed conditions, in a secure storage area with restricted access until ready for thawing and preparation as specified in the CHM. The study site will be responsible for the receipt, storage, and issue of AUTO3, and will comply with trial-specific procedures and the CHM.

AUTO3 supplied for the AUTO3-DB1 trial is specific for each patient.

7.5 ACCOUNTABILITY AND DESTRUCTION

Study drug accountability and traceability records will be maintained at the site at all times. The identification number of the patient, the administration date, batch number, expiry date and dose of AUTO3 dispensed will be recorded on the appropriate inventory forms.

The Sponsor may authorise unused AUTO3 and any product contact materials to be disposed of as standard clinical waste (typically autoclaving). The site must obtain authorisation from the Sponsor before any AUTO3 is destroyed, and AUTO3 destruction must be documented on the appropriate form. Further details can be found in the CHM. Documented evidence of destruction will be made available to the Sponsor. Ancillary supplies are not required to be returned to the Sponsor. Accurate records of all AUTO3 received at, dispensed from, returned to, and disposed of by the study site should be recorded on the ATIMP accountability log.

8 STUDY PROCEDURES AND TREATMENT

8.1 CONSENT, SCREENING AND REGISTRATION

Consent: All patients must sign an informed consent form (ICF) prior to the conduct of any study-related procedures. Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheets (PIS), are fully informed about the trial, and have confirmed their willingness to take part in the trial by signing the current approved consent form. Sites must assess a patient's ability to understand verbal and written information in English or the local language, and whether an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The Investigator, or, where delegated by the Investigator, other appropriately trained site staff, is required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved PIS for the trial should be discussed with the patient. Sufficient time must be allowed for the patient to consider and discuss participation in the trial. Written informed consent on the current approved version of the ICF for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Patient Assignment: After providing written informed consent, the patient will be issued with a unique patient identification number. The patient identification number will be used to identify the patient for the duration of the study. Patient identification numbers will not be reassigned or reused.

The screening phase begins when the first screening assessment is conducted. During the screening phase, eligibility criteria will be reviewed, demographic data obtained, and a complete clinical evaluation will be performed. Screening procedures will be performed up to 12 weeks before AUTO3 is administered (see Schedule of Assessments). If an assessment was performed as part of the patient's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed informed consent has been obtained provided that the assessments fulfil the study requirements and are performed within the specified timeframe prior to the AUTO3 administration. Retesting of abnormal screening values that lead to exclusion is allowed during the screening phase (to reassess eligibility). The measurements collected at the time closest to, but prior to, the administration of AUTO3 will be defined as the baseline values for safety assessment and treatment decisions. Adverse events associated with screening procedures will be collected. Baseline data will be collected during screening as described in the Schedule of Assessments.

Infectious Disease Screening*:* Patients will be tested by the site (in accordance with the site's Human Tissue Authority license for human application) for infectious diseases as outlined below prior to (but within 30 days of) leukapheresis. If required, an additional infectious disease test will be done on the day of leukapheresis (or within 7 days of leukapheresis). Table 13 lists the tests that must be performed as a minimum requirement.

Table 13: Infectious Disease Screening

Pathogen	Test
HIV 1 and 2	Anti-HIV-1 and 2
Hepatitis B	Hepatitis B surface antigen, anti-hepatitis B core antibody
Hepatitis C	Anti-hepatitis C virus antibody
Syphilis	Syphilis serology (chemiluminescent microparticle immunoassay)*
HTLV 1 and 2	Anti-HTLV-1 and 2

HIV=human immunodeficiency virus; HTLV=human T cell lymphotropic virus.
* A validated testing algorithm must be applied to exclude the presence of active infection with Treponema pallidum. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. A patient whose specimen tests reactive on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use.

A screening log must be maintained by the site and filed in the Investigator Site File.

PATIENT REGISTRATION: Patient registration will be performed prior to commencement of any trial treatment. Following screening evaluations , confirmation of eligibility and consent of a patient at a site, the registration form must be fully completed and then sent to Autolus Limited. The patient information will be reviewed and registration will be approved by the medical monitor.

After registration of patients, the site will coordinate with Autolus Limited on timing of leukapheresis to generate the ATIMP, AUTO3.

8.2 LEUKAPHERESIS

Following informed consent, confirmation of eligibility and registration to the study, patients will undergo an unstimulated leukapheresis for the generation of AUTO3.

Leukapheresis must be performed within 30 days of infectious disease testing and will be done following the standard institutional processes. In general, leukapheresis should be performed at least 35 days before the planned AUTO3 dosing date, as AUTO3 manufacture and release takes approximately 1 month. Based on emerging data this window may change. If required, an additional infectious disease test will be done on the day of leukapheresis (or within 7 days of leukapheresis). The leukapheresis may be repeated if an inadequate number of cells have been collected, the leukapheresate is contaminated, or additional leukapheresate is necessary for re-treatment.

The leukapheresate is the starting material for the manufacture of the ATIMP, AUTO3. The total cell number that is required for successful manufacture varies according to the dose level. Typically, a double volume leukapheresis will be performed. The target collection is 1.6×10^9 PBMCs. If the collection is insufficient, the Sponsor will advise as to the feasibility of successful manufacture. If collection is determined to be inadequate, then collected cells may be used for the Sponsor's research purposes as per the consent. The leukapheresate will be transported to the Sponsor for generation of AUTO3 at a temperature of 2 to 8°C as soon as possible and within 48 hours, ideally within 24 hours. Further details regarding this process can be found in the CHM.

Bridging chemotherapy may be prescribed to the patient during the AUTO3 manufacturing period at the discretion of the Investigator and in accordance with the exclusion criteria and

washout periods outlined in the eligibility criteria (see Section 6.2). Each leukapheresate will be identified by a unique patient identification number plus any additional patient identifiers as allowed per local regulations (typically initials and date of birth).

Upon QP release of AUTO3 product, and if the patient continues to meet the eligibility criteria for entry to the study (as outlined in Section 6), the site will liaise with the manufacturer to arrange transfer of the AUTO3 product to the participating site. Further details are provided in the CHM.

If a patient after successful leukapheresis and manufacture of AUTO3, re-enrols on the study and is eligible for treatment, repeat leukapheresis and manufacturing of AUTO3 may not be necessary and should be discussed with the Sponsor.

8.3 PRE-CONDITIONING CHEMOTHERAPY

Patients that still meet eligibility requirements for the study and in whom AUTO3 has been QP-released will proceed to receive a standard lymphodepleting pre-conditioning treatment with FLU and CY before AUTO3 infusion. Patients on Regimen B will receive modified pre-conditioning that will include a single dose of pembrolizumab. The pre-conditioning phase will begin with administration of chemotherapy and will end with the beginning of treatment with AUTO3 infusion. During this phase, AEs associated with pre-conditioning chemotherapy as well as use of concomitant medications will be collected.

Prior to administration of pre-conditioning chemotherapy, patients will undergo clinical and laboratory assessments as per the Schedule of Assessments and the site Investigator or Designee will determine if the patient is fit to receive pre-conditioning chemotherapy. If considered to be fit, patients will proceed to receive a standard lymphodepleting pre-conditioning treatment with CY and FLU for 4 days (starting Day -6), and timed to end 3 days (-1 day) before AUTO3 infusion The pre-conditioning treatment will be administered with a single dose of pembrolizumab on Day -1 for Regimen B.

8.3.1 Pre-conditioning Dose and Regimen

Fludarabine-CY dosing is described below; FLU will be given first.

Regimen **A** (Standard Pre-conditioning Regimen):

- Day -6: FLU 30 mg/m^2 followed by CY 500 mg/m^2.
- Day -5: FLU 30 mg/m^2 followed by CY 500 mg/m^2.
- Day -4: FLU 30 mg/m^2
- Day -3: FLU 30 mg/m^2.

Regimen **B** (Modified Pre-conditioning Regimen):

- Day -6: FLU 30 mg/m^2 followed by CY 500 mg/m^2.
- Day -5: FLU 30 mg/m^2 followed by CY 500 mg/m^2.
- Day -4: FLU 30 mg/m^2.
- Day -3: FLU 30 mg/m^2.
- Day -1: Pembrolizumab 200 mg.

The pre-conditioning chemotherapy should be completed a minimum of 3 days (-1 day) prior to AUTO3 infusion.

Fludarabine will be given by i.v. infusion over approximately 30 minutes in sodium chloride 0.9%. For patients with renal impairment (glomerular filtration rate 30 to 60 mL/min/1.73 m^2 [corrected]), the dose of FLU should be reduced per routine clinical practice (generally by 25%). When patients receive both CY and FLU, FLU will be given first.

Cyclophosphamide will be given by i.v. infusion over approximately 30 minutes. Adequate pre- and post-hydration for up to 4 to 6 hours (or as per institutional practice) should be given post-infusion to induce diuresis. Use of mesna for the prescribed dose is generally considered unnecessary but may be considered based on institutional practice. Cyclophosphamide dose may be reduced if the leukocyte count is <2500 cells/µL with 6 hours post-hydration.

Anti-emetic prophylaxis will be given as per standard institutional policy. Prophylaxis for tumour lysis syndrome (TLS) with allopurinol and i.v. fluids may be given if clinically necessary.

For additional information, please refer to the FLU and CY SmPCs/USPIs.

Pembrolizumab: Refer to the SmPC/USPI for additional information regarding pembrolizumab.

8.3.2 Supply of Pembrolizumab

Pembrolizumab is being used as pre-conditioning therapy prior to treatment with AUTO3. The proposed use is not an authorised indication for this drug, and duration of use for pre-conditioning therapy is limited to one dose (Regimen B) compared to continuous use until progression for other authorised indications.

Pembrolizumab is authorised and commercially available in the UK, US and EU. The Sponsor will provide appropriately labelled pembrolizumab to the hospital sites. Sufficient quantities of pembrolizumab will be dispensed to cover the prescribed dose and will be labelled for the study, and prepared as per site Standard Operating Procedures and according to manufacturer recommendations and standard local practice. Good aseptic practice must be employed when preparing pembrolizumab solutions for infusion.

8.3.3 Supply of Fludarabine and Cyclophosphamide

Fludarabine and CY are non-investigational medicinal products (NIMPs) as they are not being tested or used as a comparator in this trial. Fludarabine and CY will be used to induce lymphodepletion in the current study as a pre-conditioning treatment, prior to AUTO3 treatment. Both drugs are authorised and commercially available in the UK, US and EU. Investigators will be responsible for their own supply of FLU and CY, sourced from their institution. Sufficient quantities of FLU and CY will be dispensed to cover the prescribed dose and will be prepared as per site Standard Operating Procedures and according manufacturer recommendations. Fludarabine and CY are cytotoxic and must be handled with care in accordance with local policy. Good aseptic practice must be employed when preparing FLU and CY solutions for infusion. Further details may be found in the USPI/SmPCs for FLU and CY.

8.3.4 Accountability of Fludarabine and Cyclophosphamide and Pembrolizumab

Pharmacy records of the pembrolizumab dispensed to trial patients should be kept. The expiry date, batch number used, and manufacturer should be recorded as well as details of vials dispensed and returned.

Pharmacy records of the FLU and CY dispensed to trial patients should also be kept.

8.4 AUTO3 TREATMENT AND PATIENT MONITORING

The treatment phase will involve infusion of AUTO3 on Day 0. Patients will be monitored for up to 10 days (inpatient or ambulatory care setting), or longer if clinically necessary.

8.4.1 Assessment Prior to AUTO3 Infusion

Prior to administration of AUTO3 patients will undergo clinical and laboratory assessments and the site Investigator or designee will determine if the patient is eligible to receive AUTO3 as per protocol Section 6 (see Schedule of Assessments for details). For patients who receive bridging therapy, baseline disease assessment with positron emission tomography (PET)/CT should be done after completion of bridging therapy and before pre-conditioning and AUTO3 infusion.

If patients are not eligible to receive infusion of AUTO3 (Section 6.2), the infusion will be delayed. Infusion at a later date may be performed as per dose delay guidelines (Section 8.4.4) or cancelled.

8.4.2 AUTO3 Administration

AUTO3 (upon successful QP release) will be administered as a single rapid i.v. infusion on Day 0 in an in-patient setting. Full details will be provided in the CHM. Only the Investigator or Investigator's designee will dispense the study product.

Premedication with diphenhydramine/chlorpheniramine and paracetamol/acetaminophen may be given prior to infusion of AUTO3 as per standard institutional practice (see Section 10.2), but steroids should not be given as part of premedication

The Investigator or Investigator's designee or a study research nurse experienced in the administration of cellular blood products as per the trial-specific procedure will verify that the patient details (Unique Patient Number) on the AUTO3 label matches the recipient, check the dose of cells, volume, and number of cryobags to be infused and prescribe the AUTO3 on a blood product chart. Details of the exact dose, volume (from label), time of completion of thawing and time of completion of infusion will be documented in the applicable study records.

AUTO3 will be infused as described in the CHM. In brief, AUTO3 will be thawed in a 37°C water bath under sterile conditions, the bag will be gently massaged until the cells have just thawed. There should be no frozen clumps left in the bag. The entire contents of the bag will be given as an i.v. infusion using a syringe or gravity aided infusion through a central or peripheral venous line over **5 to 15 minutes** (max under 30 mins) through an 18-gauge blood set. **A leukodepleting filter must NOT be used for the infusion of the T cell product.** The infusion line and the bag should be flushed as described in the CHM to ensure all cells have

been administered. If the AUTO3 cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused.

Although not routinely practiced, there may be circumstances (e.g. when AUTO3 is administered by a site for the first time), when Sponsor representatives may be present to observe the thawing and/or dosing of AUTO3. These individuals will have no participation in the preparation of the product nor in any part in the patient's medical care. This will only occur if the practice is allowed by local IRB Ethics Committee and institutional guidelines and the consent of the patient. This may also allow the sponsor to collect best practices and further refine dose administration.

The time between completion of thawing and completion of infusion should not exceed 30 minutes.

8.4.3 Monitoring During and After Drug Administration

8.4.3.1 During Phase I – Escalation

Patients will be monitored (inpatient or ambulatory care setting) for up to 10 days (or until all AUTO3 related non-haematological toxicities have returned to Grade ≤1 or baseline) following the cell infusion (longer if clinically necessary). Monitoring will include temperature, pulse, blood pressure, respiratory rate, and oxygen saturations immediately prior to and every 30 minutes (±10 minutes) for 4 hours after AUTO3 infusion. Any clinically significant changes in vital signs should be recorded and reported as an AE as appropriate. In the event of allergic adverse reactions, anti-histamines may be administered, as well as oxygen and salbutamol in the event of respiratory distress.

During hospitalisation/ambulatory care, patients will be monitored daily and will undergo blood tests (see Schedule of Assessments) for signs of toxicity, in particular for CRS, TLS and neurological disturbance. Transfusions of blood products, antibiotics, analgesics, and intensive care will also be provided as clinically indicated. Prophylaxis for TLS may be initiated if the risk is considered high or for all new patients if TLS occurs at a certain dose level. Urate levels will be monitored and treatment started if indicated.

Data regarding intensity of care will be collected on a periodic basis e.g. duration of inpatient stay or ambulatory care admission, intensive care unit/intensive therapy unit stay, duration of pressor support, mechanical ventilation, dialysis.

Patients may be discharged from hospital when clinically appropriate or following successful management of CRS, even if it is prior to 10 days post-AUTO3 infusion, if deemed appropriate by the treating Investigator. The in-patient stay may be extended if deemed necessary by the treating physician.

Following discharge from the hospital, the patient will be closely monitored for AEs and laboratory abnormalities, at least on a weekly basis. The required study procedures and assessments to be conducted during the Treatment Stage are outlined in the Schedule of Assessments. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. Provided that all criteria are satisfied (see Section 8.4.7), patients may receive re-treatment (2nd cycle) of AUTO3.

Patients will also receive consolidation treatment (Section 8.5). Patients will be monitored (inpatient or ambulatory care setting) for up to 3 days after the first dose of consolidation treatment with pembrolizumab on Day 14 (applicable to Regimen A). Safety and efficacy

assessments described in the Schedule of Assessment will be performed and AEs and concomitant medications will be documented.

After being discharged, patients will attend the clinic on a regular basis as described in the Schedule of Assessments (Table 1). At the end of the treatment phase (Day 28), a complete evaluation of disease response will be performed as outlined in Schedule of Assessments Table 1 and described in Section 9.4. Clinical evaluations and laboratory assessments may be repeated more frequently including neurological examination and coagulation as clinically indicated.

After completing the study the patients will be followed on a separate long-term follow-up protocol (AUTO-LT1).

8.4.3.2 During Phase I Expansion Cohort

Patients will be infused and monitored in an outpatient/ambulatory care setting. The monitoring guidelines are the same as described in Section 8.4.3.1, except during the 10 days following AUTO3 infusion, the patients are assessed by a healthcare professional at a minimum every 2 to 3 days instead of daily. In addition, it is recommended for the patient to have a daily verbal communication with qualified nurse/medical personnel (phone call). **Note:** in the UK, the patients are to be assessed at least once a day for 10 days by a physician or qualified designee. Based on emerging safety finding patients may be admitted as deemed appropriate by the medical personnel.

8.4.4 Dose Delay

If the pre-conditioning regimen is interrupted for intercurrent illness or other reasons, the patient may complete or recommence the pre-conditioning regimen after recovery, or proceed with partial pre-conditioning according to the Investigator's judgment after consultation with the Sponsor. Patients will be closely monitored during and after the conditioning regimen.

If a patient is unable to be dosed on the planned day with AUTO3, they may undergo delayed dosing, and be re-pre-conditioned (if appropriate) if they continue to meet the study enrolment criteria. If AUTO3 infusion is delayed and time between end of pre-conditioning chemotherapy and AUTO3 infusion is more than 8 days, infusion of AUTO3 should not proceed without consultation with the Sponsor. Imaging studies may not need to be repeated if the patient has not received any other anti-lymphoma therapy in the interim (excluding steroids and pre-conditioning chemotherapy). Patients undergoing delayed dosing may be evaluable for dose escalation decision making if the SEC so concludes.

If the patient is deemed unsuitable to receive AUTO3, they will be discontinued from the clinical trial (see Section 15.2) and replaced. Each case will be discussed with the Sponsor.

Dose delays with pembrolizumab should be managed as per the prescribed dosing windows in the protocol and SmPC/USPI.

8.4.5 Interruption of Infusion

In the event of severe infusion reaction, the FLU-CY or AUTO3 or pembrolizumab infusion should be stopped and the patient treated as clinically indicated. When the patient has recovered, the infusion may be restarted.

Interruption of AUTO3 should not be greater than 30 minutes after thawing of AUTO3. If an infusion is interrupted for mechanical, technical or any other reason, then this should be dealt with per local practice and the infusion restarted as soon as possible. In case of uncertainty, individual cases should be discussed with the Sponsor.

If the patient develops an allergic reaction to the drugs in the pre-conditioning regimen, alternative drugs as per the institutional practice may be considered after discussion with the Sponsor.

8.4.6 Duration of Treatment

In most patients, it is expected that AUTO3 will be given once. However, if a patient has sufficient AUTO3 remaining from the original manufacture and meets the re-treatment criteria, a second treatment may be given (see re-treatment of patient Section 8.4.7).

8.4.7 Re-treatment of Patients

It is expected that most patients will receive a single dose of AUTO3 as part of their treatment. However, some patients may have sufficient AUTO3 leftover for a re-treatment, or leukapheresate, which can be used to manufacture AUTO3, or they may be eligible for repeat leukapheresis. Such patients may receive a re-treatment (as single infusion) of their own stored AUTO3. Prior to re-treatment, the patient needs to meet the following criteria:

1. Patient shows evidence of low AUTO3 survival ($<0.2 \times 10^9$/L) and no significant anti-tumour effect (no CR) after the first dose, and the first treatment dose is considered to be sub therapeutic.

OR

2. There was objective clinical evidence of anti-tumour activity following the previous AUTO3 infusion (i.e. Stable Disease or better).

OR

3. The patient has evidence of progressive disease in the context of declining levels of AUTO3. Circulating levels AUTO3 cells must be low ($<0.2 \times 10^9$/L) for at least 2 weeks prior to the second infusion.

AND all of the following:

4. The patient has adequate cryopreserved AUTO3 available for a second dose (≤highest safe dose).

5. The patient tolerated the first infusion without dose-limiting or other severe or unmanageable toxicity for a follow-up period of at least 28 days.

6. The patient still fulfils the trial entry criteria required to tolerate another pre-conditioning treatment and AUTO3 infusion.

Patients undergoing a second AUTO3 infusion should receive the same pre-conditioning. The dose of AUTO3 can be at (or up to) the highest dose level cohort that has been declared safe after dosing at least three patients and has shown evidence of anti-tumour activity (CR or PR). These patients who are being re-treated will not contribute to dose escalation decisions in that dose cohort, unless a DLT occurs as per DLT criteria in Section 3.6. Patients that have or have not received consolidation or pre-conditioning therapy with anti-PD-1 antibody with the earlier

dose may receive consolidation or pre-conditioning following re-treatment with AUTO3. Depending on the number of cells available, an intermediate dose may also be administered if considered appropriate. The decision to re-treat a patient will be made by the treating Investigator and Sponsor in consultation with the SEC. Patients re-treated will be monitored in a similar way to patients being treated for the first time.

8.5 CONSOLIDATION THERAPY

Anti-PD-1 Antibody: Pembrolizumab

Consolidation therapy with anti-PD-1 antibody pembrolizumab will be administered after AUTO3 and following resolution of key toxicities such as CRS (resolution to ≤ Grade 1) and NT.

8.5.1 Pembrolizumab Dose and Regimen

Pembrolizumab (200 mg) will be infused over 30 minutes:

- on Day 14 (±3 days) and repeated every 3 weeks for a total of 3 doses i.e. on Day 35 (±3 days) and Day 56 (±3 days) (Regimen A only)

Administration of pembrolizumab may be delayed by up to 14 days until any ongoing CRS or NT has resolved, with a minimum dosing interval of 21 days between doses.

Based on emerging data, the Investigator may consider additional doses on a case-by-case basis and in consultation with the medical team. Pembrolizumab should be prepared and infused in accordance with the USPI/SmPC.

Administration of pembrolizumab should be withheld if any of the following occur:

- ≥Grade 2 pneumonitis.
- ≥Grade 2 colitis.
- ≥Grade 3 endocrinopathies.
- ≥Grade 2 nephritis.
- Aspartate aminotransferase or alanine aminotransferase >3 and up to 5 × ULN or total bilirubin >25 µmol/L (1.5 mg/dL) and up to 3 × ULN.
- Any other severe or Grade 3 treatment-related adverse reaction.

Refer to the SmPC/USPI for additional information regarding pembrolizumab.

8.5.2 Supply of Pembrolizumab

Pembrolizumab is being used as consolidation therapy following treatment with AUTO3. The proposed use is not an authorised indication for this drug, and duration of use for consolidation therapy is limited to three doses in total, with one dose every 3 weeks (Regimen A) and one dose in Regimen B (compared to continuous use until progression for other authorised indications).

Pembrolizumab is authorised and commercially available in the UK, US and EU. The Sponsor will provide appropriately labelled pembrolizumab to the hospital sites. Sufficient quantities of pembrolizumab will be dispensed to cover the prescribed dose and will be labelled for the

study, and prepared as per site Standard Operating Procedures and according to manufacturer recommendations and standard local practice. Good aseptic practice must be employed when preparing pembrolizumab solutions for infusion.

8.5.3 Accountability of Pembrolizumab

Pharmacy records should be kept of the pembrolizumab dispensed to trial patients. The expiry date, batch number used, and manufacturer should be recorded as well as details of vials dispensed and returned.

8.6 FOLLOW-UP PHASE

Upon completion of consolidation treatment, for patients enrolled in Phase I in regimen A, or 1 month after administration of AUTO3 for patients enrolled in Phase I regimen B and Phase II, all patients will enter the follow-up phase where they will continue to be monitored periodically as detailed in the schedule of assessments until the end of the study or until early withdrawal or death, whichever is the latest for the assessment of anti-tumour response and for safety evaluation. Adverse events that are considered related to the study medication will be recorded/reported as detailed in Section 12.3.

8.6.1 Efficacy and Safety Follow-up

Following initial achievement of CR, stable disease, PR (and non-evaluable [NE] patients) at Month 1 or later, based on PET using [^{18}F]-fluorodeoxyglucose (FDG), CT scans, magnetic resonance imaging (MRI), physical examination, including lymphoma B-symptoms, BM, and other procedures as appropriate, the patients will be followed up for efficacy and safety.

Patients will have periodic monitoring of response (as per Appendix 1) based on PET using [^{18}F]-FDG, CT scans, magnetic resonance imaging (MRI), as described in the schedule of assessments.

Patients who proceed to transplant or other anti-cancer therapies while in remission will also be monitored for efficacy and safety until the EOS.

Patients will be invited to participate in the long-term follow-up study at EOS.

Relapse evaluation: If at any time during the Efficacy and Safety Follow-Up, a patient who was in remission relapses, a full disease evaluation will be completed. As soon as possible after being aware of a relapse, the patient will be scheduled for a visit, and have PET/CT and other assessments as clinically indicated (e.g. tumour biopsy).

Once patients have completed the 36-month follow-up period post AUTO3 infusion, they will be monitored every 6 months until the end of study as per schedule of assessments (Table 2).

Patients who have received AUTO3 and who are still responding will subsequently be followed-up for:

- Survival, limited concomitant medication, all SAEs and AEs considered related to the AUTO3, AEs of special interest, and any new malignancy (Section 12.3)
- Disease response until progression or end of the study
- First subsequent therapy post-CAR-T and response if applicable
- Once a year for AUTO3 vector persistence and RCR.

8.6.2 Safety and Survival Follow-up

Patients who fail to respond to treatment or who respond but subsequently progress will continue to be monitored for safety and survival until EOS as per the safety and survival schedule of assessments (Table 3). At EOS, the patients will complete an EOS visit and will be invited to participate in the long-term follow-up study.

The first assessment for the safety and survival follow-up will happen at the next planned visit as per the safety and survival follow-up schedule of assessments e.g. if a patient progresses at Month 10, then the first visit in for safety and survival follow-up will be Month 12.

During the safety and survival follow-up, patients will come to the site as per schedule of assessments. If a patient cannot attend a scheduled visit, the information can be collected remotely (e.g. over the phone) and the Investigator should attempt at a minimum to determine the survival status and whether the patient has started receiving additional antineoplastic therapies and associated response to new treatment.

In the event that a patient still in remission is no longer willing to be followed up for efficacy and safety, but agrees to remain on study to be monitored for safety and survival until completion of the study, the Investigator should attempt at a minimum to determine the relapse status and whether the patient has started receiving additional antineoplastic therapies. The efficacy data collected as per the local standard of care may be recorded in the clinical database until they relapse or rollover to the long-term follow-up study.

Selected AEs and concomitant medications will be recorded, please refer to Section 12.3.

For patients who are lost to follow-up, the Investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Once patients have completed the 36-month follow-up period post AUTO3 infusion, they will be monitored every 6 months until the end of study as per schedule of assessments.

Patients who have received AUTO3 and subsequently progressed will be followed up for:

- Survival, all SAEs and AEs considered related to AUTO3, AEs of special interest and any new malignancy (see Section 12.3)
- First subsequent therapy post-CAR-T and response if applicable
- Once a year for AUTO3 vector persistence and RCR

If a patient misses a scheduled visit, or if the visit time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact with the patient or correspondence with local health care provider.

Any patient who had already completed their end of study visit on the main AUTO3-DB1 study may be re-enrolled if they wish to consent to the new schedule of assessments for long-term safety and survival follow-up (Table 3).

8.7 LONG-TERM FOLLOW-UP

The aim of the long-term follow-up protocol is to assess for delayed consequences due to the use of a viral vector during the manufacture of AUTO3. Semi-annual and annual evaluations will be performed on all patients who have received AUTO3. At least once a year, patients will visit the clinic for a physical exam and medical history (including concomitant medications

and AEs) with careful attention to features possibly related to retrovirus associated events such as new malignancies, new incidence or exacerbation of autoimmune disorder. In addition, blood samples will be taken to evaluate routine safety endpoints, CAR-T persistence and RCR.

All patients who have received AUTO3 will be eligible and asked for their consent to be enrolled onto a separate long-term follow-up protocol at EOS.

Patients enrolled in the long-term follow-up study will be monitored for all SAEs considered related to the study treatment, AEs of special interest, including any new malignancy, for a period of up to 15 years following treatment with AUTO3. Data regarding survival and subsequent therapies will be collected.

9 STUDY ASSESSMENTS

9.1 DEMOGRAPHIC AND BASELINE ASSESSMENTS

The following will be collected at screening to determine eligibility and baseline status of the patient.

9.1.2 Demographic Data and Baseline Variables

Demographic data

- Demographic data will include self-reported race/ethnicity, age, gender, and height at screening visit prior to leukapheresis.

Medical history/lymphoma

- Medical history includes clinically significant diseases, surgeries, lymphoma history and treatment, lymphoma B-symptoms, all medications used by the patient and known allergies. Histological confirmation of disease diagnosis will be obtained (pathology report).

Pregnancy test

- Serum (β-human chorionic gonadotropin) or urine pregnancy testing will be performed for females of childbearing potential at the screening visit and will be repeated when the patient is admitted prior to starting lymphodepletion, prior to starting pre-conditioning treatment, and prior to AUTO3 infusion. Following AUTO3 infusion, pregnancy testing will be performed at Day 28, Day 56, Month 3, Month 6, Month 12, Month 18 and Month 24 (for patients on study), as described in the Schedule of Assessments.

9.2 SAFETY EVALUATIONS

All patients who receive AUTO3 will be considered evaluable for toxicity assessment. Any clinically relevant changes occurring during the study must be recorded on the AE section of the electronic Case Report Form (eCRF). Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, clinical laboratory tests, and performance status assessments at specified time points as described in the Schedule of Assessments. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the Investigator until resolution, or until a clinically stable endpoint is reached. The study will be monitored by the SEC and IDMC (details regarding the SEC and IDMC are provided in Section 13). The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Assessments.

9.2.1 Adverse Events and Toxicity

Adverse events will be noted by clinic staff or reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally acceptable representative) for the duration of the study. Adverse event recording and reporting is described in detail in Section 12.3.

Toxicity will be graded using the NCI CTCAE Version 5.0 criteria. The incidence of NCI Grade 3 to 5 toxicity and the frequency and severity of AEs occurring within 75 days of AUTO3 infusion will be determined. In particular, the incidence of Grade 3 to 5 CRS and

Grade 3 to 5 NT occurring within 75 days of AUTO3, according to the ASTCT/ASBMT consensus grading (Lee et al. 2019) will be determined (see Section 12).

The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

9.2.2 Clinical Laboratory Tests

Blood samples for haematology, coagulation and biochemistry will be collected at each visit as specified in the Schedule of Assessments. Where appropriate, tests must be performed prior to receiving pre-conditioning treatment or AUTO3 infusion. More frequent clinical laboratory tests may be performed if indicated by the overall clinical condition of the patient or by abnormalities that warrant more frequent monitoring. Screening laboratory results must be available to the Investigator for evaluation before AUTO3 infusion and subsequent laboratory results should be available at the time of the patient's evaluation by the treating physician. The Investigator must review the laboratory reports, document this review, and ensure that any clinically relevant changes occurring during the study are recorded in the AE section of the eCRF. The laboratory reports must be filed with the source documents. A summary of the tests that will be performed by the local laboratory is presented in Table 14.

Table 14: Clinical Laboratory Tests

Assessment	Description
Haematology	Haemoglobin, red blood cell count, platelet count, white blood cell count with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils).
Coagulation	Prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen.
Biochemistry	Sodium, phosphate, potassium, ALT, AST, uric acid, urea, creatinine, CPK, lactate dehydrogenase, total bilirubin, calcium, albumin. All tests must be performed prior to AUTO3 infusion on Day 0.
Ferritin, C-reactive protein	Ferritin, C-reactive protein.
Pregnancy test	Serum (β-human chorionic gonadotropin) or urine pregnancy testing for females of childbearing potential.
Serology (at screening only)	• HIV antibody. • Hepatitis B core antibody: if positive, further testing (DNA by PCR) to rule out active disease or chronic carrier. Must be confirmed negative prior to screening. • Hepatitis C virus antibody: if positive for hepatitis C virus, further testing (by ribonucleic acid PCR) should be performed to rule out active infection. • Anti-HTLV-1. • Anti-HTLV-2 • Syphilis Serology

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; DNA=deoxyribonucleic acid; HIV=human immunodeficiency virus; HTLV=human T cell lymphotropic virus; PCR=polymerase chain reaction.

9.2.3 12-lead Electrocardiogram

A 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and corrected QT intervals. Refer to the Schedule of Assessments for details regarding the frequency of ECG assessments. At each time point, a

single 12-lead ECG will be performed by qualified site personnel. The clinical Investigator or designee will review the printout, including ECG morphology. The ECG should be repeated in triplicate if motion artefacts or clinically relevant abnormalities are noted. Additional cardiovascular assessments should be performed as clinically appropriate to ensure patient safety. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, then blood draw.

9.2.4 Echocardiogram and Multigated Acquisition

Echocardiogram is the preferred method to assess cardiac ejection fraction and cardiac valve abnormalities; MUGA is an acceptable alternative. Assessments should be performed at screening and additional assessments may be performed at the onset of CRS and/or when clinically indicated. Generally, for a patient, the same procedure should be performed at screening and at any follow-up assessment to allow direct comparison.

9.2.5 Vital Signs

Vital signs will include temperature, pulse/heart rate, respiratory rate, blood pressure (systolic and diastolic), oxygen saturation and weight. Blood pressure and pulse/heart rate measurements should be recorded with the patient in a seated position or supine. Multiple time points (a minimum of three) will be collected prior to treatment to establish a good baseline blood pressure for the patient. Blood pressure and pulse/heart rate measurements will be assessed with an automated device. Manual techniques will be used only if an automated device is not available.

9.2.6 Physical Examination

A complete physical examination will be conducted at screening as per the institutional standard practice. Thereafter, a symptom-directed physical examination will be conducted at subsequent visits. The schedule for physical examinations is provided in the Schedule of Assessments. Any clinically significant observations will be recorded and reported as an AE as appropriate.

9.2.7 ECOG Performance Status

The ECOG scale provided in Appendix 2 will be used to grade changes in the patient's daily living activities. The frequency of ECOG assessments is provided in the Schedule of Assessments.

9.3 PHARMACODYNAMICS AND BIOMARKER EVALUATION

Blood-based pharmacodynamics biomarkers will be evaluated in all patients as described in the Schedule of Assessments. Peripheral blood biomarkers may be assessed pre- and post-AUTO3 treatment. Assessment at additional time points may be performed based on emerging data to better understand the safety/efficacy of the CAR product. Details regarding sample collection and processing are provided in the lab manual.

9.3.1 Evaluation of AUTO3 Persistence in Peripheral Blood and Bone Marrow

Two validated assays will be used to measure the expansion/persistence of CD19/CD22 CAR-positive T cells at the time points indicated in the Schedule of Assessments. Flow cytometry will be used to measure the frequency of CD19/CD22 CAR-positive T cells per microliter of whole blood and/or a polymerase chain reaction (PCR) assay will be used to quantify the number of copies of the CD19/CD22 CAR transgene per microgram of genomic deoxyribonucleic acid (DNA) or per 100 cells in peripheral whole blood. Please refer to the AUTO3-DB1 laboratory manual for the handling and storage of samples.

9.3.2 Evaluation of RCR in Peripheral Blood

As per Health Authorities' guidelines, tests will be performed to evaluate and monitor the presence of RCR by PCR in whole blood or PBMCs. Please refer to the AUTO3-DB1 laboratory manual for the handling and storage of samples.

9.3.3 Insertional Mutagenesis

Blood samples will be stored and archived before and after treatment (per Schedule of Assessments) with the intent to be analysed for insertional mutagenesis, should a patient develop a new malignancy. The result will allow identification of any potential relationship between AUTO3 treatment and the development of any new malignancy. Please refer to the AUTO3-DB1 laboratory manual for the handling and storage of samples.

9.3.4 B Cell Aplasia (Flow Cytometry)

Blood samples will be collected for flow cytometry of B cells in accordance with the Schedule of Assessments for the assessment of B cell aplasia. Samples will be analysed in local hospital laboratories as per local practice.

9.3.5 Serum IgG Levels

Blood samples will be collected in accordance with the Schedule of Assessments for the measurement of serum IgG, IgA and IgM levels. Samples will be analysed in local hospital laboratories.

9.3.6 Immunogenicity Analysis

Detection of human anti-CAR T cell responses and antibodies, or related antibodies, may be measured in cryopreserved PBMCs and serum. Serum or plasma samples at selected time points, for example at Day 0, end of DLT evaluation period and Month 6, may be analysed if clinically indicated. Additional samples may be analysed if clinically indicated e.g. if AUTO3 cells become undetectable or at relapse. The assays have not yet been developed but will be based on assays used to measure human anti-human antibodies in patients treated with monoclonal antibodies or on assays to measure T cell responses in cell therapy trials. The development of the assays may utilise plasma, serum or PBMCs collected during the trial, and data will not be reported if a suitable assay cannot be developed.

9.3.7 Exploratory Biomarker Assessments

Serum cytokine profile: The serum cytokine profile (using a minimum dataset of TNF-α, IFN-γ, and IL-6) will be measured using a highly sensitive, reproducible, and validated cytokine assay at time points indicated in the Schedule of Assessments. Additional samples may be taken where clinically indicated, for example during CRS. Blood samples for cytokine measurements may be frozen and batched for analysis or assayed using fresh serum. Serum may also be used for measurement of other biomarkers as appropriate.

Immunological/genomic phenotyping: PBMCs will be isolated from whole blood following standard procedures and cryopreserved in liquid nitrogen for later immunological assessment or assessed immediately. Samples will not be stored for more than 15 years. PBMCs may be used for various immunological assessments such as phenotyping by flow cytometry, genomic analysis and other assays as developed. Immunophenotyping or genotyping of PBMCs will be evaluated at selected time points (per Schedule of Assessments) and dependent upon a minimum frequency of CD19/CD22 CAR-positive cells.

Biomarker expression: The expression of PD-L1, CD19 and CD22 or other immunological markers on lymphoma cells and/or the presence of CAR T cells will be evaluated by IHC and/or flow cytometry in available tissue (blood, BM, tumour tissue).

If a patient is declared to have disease progression outside of scheduled time points, optional blood and tissue samples will be collected to help elucidate the reasons for primary or acquired resistance using appropriate methods.

CSF Evaluation: CSF may be investigated for cytokine levels and/or evidence of tumour cells or CAR T cells or other parameters that may be determined by emerging data.

9.4 EFFICACY EVALUATION

Response evaluations will be conducted as specified in the Schedule of Assessments and will include the following: PET using [^{18}F]-fluorodeoxyglucose (FDG), CT scans, magnetic resonance imaging (MRI), physical examination, including lymphoma B-symptoms, BM, and other procedures as necessary. Examinations such as endoscopy may be performed if there is GI involvement at baseline. These assessments should be performed throughout the study at each time point using the same method of assessment used to assess disease at baseline. The baseline assessment should be performed within 35 days of starting pre-conditioning (approximately 40 days before receiving AUTO3). Patients receiving bridging therapy should have the baseline disease assessment after the bridging therapy is completed and prior to starting pre-conditioning. Response to treatment will be assessed by the Investigator at the site and the results will be recorded in the eCRF.

It is important that instances and evidence of disease progression be reported to the Sponsor as soon as possible. The medical monitor will review the data to confirm that the criteria for disease progression have been met. If the medical monitor concurs, the Investigator will be notified and the patient will be withdrawn from the study. Whenever possible, subsequent anti-cancer treatment should start once disease progression has been confirmed.

9.4.1 PET Scan

Positron emission tomography using [^{18}F]-FDG is important for the complete assessment of response and progression. Whole body [^{18}F]-FDG-PET scan (skull base to the proximal femur)

is mandatory at screening; during the study PET scans will be performed as per the Schedule of Assessments. For patients who achieve a complete metabolic response (CMR), disease assessments after Month 6 can be based on CT scans alone, if clinically appropriate. If relapse occurs after CMR or disease progression is suspected (e.g. new or enlarging lesion(s) detected on CT scan), a PET scan is to be repeated to confirm relapse/progression.

Assessment of PET results is based on published criteria. Visual assessment is considered adequate for determining whether a PET scan is positive, and use of the standardised uptake value is not necessary. A positive scan is defined as focal or diffuse [^{18}F]-FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardised uptake value cut-off. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased [^{18}F]-FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with [^{18}F]-FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased BM uptake within weeks after treatment.

During the study, disease response will be assessed using CT scans as per the Schedule of Assessments with i.v. contrast of the neck, chest, abdomen, pelvis and any other location where disease was present at screening, and whole body [^{18}F]-FDG-PET scans. Patients who are intolerant of i.v. CT contrast agents will have CT scans performed with oral contrast.

A separate CT scan and PET scan are preferred, but if the only available modality is combined/dual PET/CT scanner, then the CT portion of a PET/CT may be used in lieu of a dedicated CT; CT scanning must be done according to certain imaging requirements that ensure that an optimised CT examination is done.

Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI is only required if clinically indicated.

Disease assessments will be performed as outlined in the Schedule of Assessments and scans/images will be collected and assessed by independent central review (Phase II only).

9.4.2 Bone Marrow Assessment

Bone marrow aspirate is mandatory and biopsy is optional at screening. Patients with BM involvement at baseline must have a repeat BM evaluation at the time of CR (preferably within 30 days of the initial documentation of CR). If BM involvement can be confirmed with morphology, IHC need not be performed. Only one BM examination is necessary for complete documentation of the CR.

Portions of the BM aspirates collected at screening and at CR (if aspirate is collected at CR) may be used to for biomarker assessment such as persistence of CD19/CD22 CAR-positive T cells in the marrow, PD-L1 expression, and minimal residual disease.

9.4.3 Physical Examination

Patients should have physical examination to evaluate possible presence of palpable lymph nodes, tumour masses or enlargement of spleen and liver at screening and other time points as specified in the Schedule of Assessments. Symptom-directed questions should be asked to evaluate for presence of lymphoma B-symptoms.

9.4.4 Efficacy Criteria

9.4.4.1 Assessment of Disease Response and Progressive Disease

Efficacy assessments for the purpose of the study result analyses will be performed by the Investigators and independent central radiology review (Phase II only) according to the Lugano Classification (Cheson et al. 2014) (Appendix 1). The primary efficacy analysis for Phase II will be based on the independent central review.

9.4.4.2 Appendix 1(Younes et al. 2017)(Cheson et al. 2014)Definition of Measurable and Assessable Disease

Eligible patients must have PET-positive disease at baseline (FDG-avid disease corresponding with a 5-point scale score of 4 or 5). Patients who receive bridging therapy after study enrolment must have a PET/CT scan performed after completion of bridging therapy. Patients who do not have PET-positive disease (5-point scale score of 4 or 5) after bridging treatment will be excluded from the primary efficacy analysis. Patients with PET-positive disease at baseline but without measurable disease per CT scan will be included in the primary efficacy analysis.

For radiological assessments based on CT scan (or MRI), measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. Each measurable site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement, or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in two perpendicular dimensions. Measurement must be determined by imaging evaluation. All other sites of disease are considered assessable, but not measurable. Up to six measurable sites of disease, clearly measurable in two perpendicular dimensions, will be followed for each patient. Measurable sites of disease should be chosen such that they are representative of the patient's disease (this includes splenic and extranodal disease). If there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm in two perpendicular dimensions, at least one lymph node mass from each region should always be included. In addition, selection of measurable lesions should be from as disparate regions of the body as possible.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary, but is not measurable as defined above. Examples of assessable disease include bone lesions; mucosal lesions in the GI tract; effusions; pleural, peritoneal, or bowel wall thickening; disease limited to BM; and groups of lymph nodes that are not measurable but are thought to represent lymphoma. In addition, if more than six sites of disease are measurable, these other sites of measurable disease may be included as assessable disease.

9.4.4.3 Endpoints

The efficacy endpoints are ORR, DOR, PFS, and OS:

Overall response rate: Complete response or PR by the Criteria for Response Assessment of NHL (i.e. Lugano Classification)

The proportion of patients achieving PR and CR at 1, 3, and 6 months post-AUTO3 infusion will also be determined.

Duration of response (DOR): DOR is defined as the time from the first observed CR or PR to documented disease progression or death due to underlying disease, for patients who are considered as responders. DOR will also be evaluated for CR and PR patients separately.

Progression-free survival: PFS is defined as the time from first treatment of AUTO3 to documented disease progression or death due to any cause.

Overall survival: OS is defined as the time from the first treatment of AUTO3 to death due to any cause.

9.5 BLOOD VOLUME COLLECTIONS

In general, blood will be taken from a Hickman line or other central venous access for the first year after AUTO3 infusion so that venepuncture will not be needed. The maximum volume of blood collected for study related assessments on any one day is unlikely to exceed 76 mL. Additional samples may be collected as required to ensure the safety of the patient. Refer to the laboratory manual for the handling and storages of samples.

10 GUIDELINES FOR PREVENTION, MONITORING, AND MANAGEMENT OF ADVERSE EVENTS

The following guidelines are recommendations and should be modified according to local practice and the patient's clinical need.

10.1 GENERAL SUPPORTIVE CARE GUIDELINES FOR PATIENTS RECEIVING CAR T CELL THERAPY

Table 15: General Supportive Care Guidelines for Patients Receiving CAR T Cell Therapy

Toxicity	Preventive and Supportive Care Interventions
General	Administer paracetamol/acetaminophen for symptomatic management of fevers in patients with normal hepatic function;
	Provide cooling blankets for fevers >40°C;
	Appropriate personnel and appropriate resuscitation equipment should be available in or near the infusion room and a physician should be readily available during the infusion of study drug;
	Tocilizumab must be available at sites managing patients receiving CAR T cell products;
	Avoid corticosteroids and, if thrombocytopenic, NSAIDs.
Infection Prophylaxis	Patients should receive prophylaxis with antimicrobials due to the use of FLU and the potentially extended duration of lymphopenia and neutropenia; Patients should receive pneumocystis prophylaxis with trimethoprim-sulfamethoxazole or suitable alternative agents, and either acyclovir or valacyclovir for herpes virus prophylaxis from the start of conditioning chemotherapy until 3 to 6 months post-AUTO3 infusion; Additional anti-microbial (e.g. ciprofloxacin) and anti-fungal prophylaxis to be given as per institutional practice; All patients should be monitored for CMV by PCR weekly during admission or as necessary; All patients with fevers while neutropenic must have blood cultures drawn and receive broad-spectrum antibiotics as per institutional practice.
Respiratory	Monitor for oxygen saturation at every visit, a significant decrease in oxygen saturation at room air should be investigated and managed with supportive care including supplemental oxygen, anti-microbials and ventilator support as appropriate. Patients with an oxygen requirement of >40% (or lower based on emerging data) in setting of CRS should receive treatment with tocilizumab (see Section 10.4).

Toxicity	Preventive and Supportive Care Interventions
Cardiovascular	Stop or taper antihypertensive medications prior to cell infusion;
	Monitor vital signs at least every 12 to 24 hours on an inpatient unit during hospital stay;
	Monitor vital signs every 2 hours in patients with fevers and tachycardia;
	Initiate replacement i.v. fluids for patients with poor oral intake or high insensible losses to maintain net even fluid balance;
	Administer i.v. fluid boluses for patients with systolic blood pressure less than their pre-infusion baseline;
	Patients with a systolic blood pressure <80% of their pre-infusion baseline and <100 mmHg (or as age appropriate) receive a 1 litre normal saline bolus;
	Patients with a systolic blood pressure <85 mmHg (or as age appropriate) receive a 1 litre normal saline bolus regardless of baseline blood pressure;
	Patients receiving >1 i.v. fluid bolus (or as age appropriate) for hypotension or patients in the intensive care unit for toxicity management have a serum troponin drawn, and an ECG and an ECHO performed to evaluate for cardiac toxicity (see Section 10.4);
	Norepinephrine is the preferred first-line vasopressor for patients with hypotension initiated on vasopressor support.
Haematologic	Initiate allopurinol for TLS prophylaxis in patients without a contraindication prior to pre-conditioning chemotherapy; if indicated (see Section 10.7);
	Transfuse packed red cells for goal haemoglobin of ≥80 g/L;
	Transfuse platelets for a goal platelet count of ≥20,000/µL;
	Monitor complete blood count with differential at least daily. When absolute neutrophil count decreases to <500/µL; initiate granulocyte-colony stimulating factor support. Continue until absolute neutrophil count increases to ≥1500 µL;
	Transfuse fresh frozen plasma with a goal of normalisation of PTT in patients with a partial thromboplastin time (PTT) >1.5-fold above the ULN; and
	Transfuse cryoprecipitate to maintain fibrinogen of ≥100 mg/dL if the patient is at risk of bleeding. If the patient is bleeding, a higher level of fibrinogen should be maintained.
Neurologic	The nursing staff conducts focused neurologic examinations at least every 4 to 6 hours in patients experiencing neurologic toxicity (see Section 10.6);
	Perform brain MRI in any patient experiencing neurologic toxicity;
	Perform lumbar puncture to evaluate for infectious pathogens, cytokine levels, and CAR T cell levels in patients experiencing neurologic toxicity whenever feasible;
	Consider a neurology consultation for any patient experiencing neurologic toxicity; and
	Standard antiepileptic medications for patients with active seizures. Prophylactic antiepileptic medications are not required.

CAR=chimeric antigen receptor; CMV=cytomegalovirus; ECG=electrocardiogram; ECHO=echocardiogram; i.v.=intravenous; MRI=magnetic resonance imaging; NSAIDs=non-steroidal anti-inflammatory drugs; PCR=polymerase chain reaction; PTT=partial thromboplastin time; TLS=tumour lysis syndrome; ULN=upper limit of normal.
Taken from: (Brudno and Kochenderfer 2016).

10.2 PRE- AND POST-CAR T INFUSION SUPPORTIVE THERAPY

AUTO3 is an autologous product, with humanised scFv CARs and is less likely to be immunogenic and induce an infusion or hypersensitivity reaction compared to murine scFv CARs. However, the following medications should be given 30 minutes before the study drug infusion: oral paracetamol/acetaminophen and an antihistamine (diphenhydramine/ chlorpheniramine or equivalent). These medications may be discontinued based on emerging data. In addition, pre-infusion medications listed in Table 16 may also be administered if necessary.

Post-infusion medication listed in Table 16 may be considered following FLU-CY or AUTO3 infusion if necessary, and such medication(s) may be continued for up to 48 hours after the infusion. Use of additional supportive care measures may be instituted as clinically necessary at the discretion of the Investigator.

Table 16: Pre- and Post-infusion Medications

Medication	Dose	Administration	Pre-infusion	Post-infusion
Antihistamine	Diphenhydramine/chlorpheniramine (10 to 20 mg) or equivalent.	Oral – administer at least 1 hour prior to study drug. I.v. or as appropriate – administer at least 30 minutes prior to study drug.	Yes	Optional
	Diphenhydramine/chlorpheniramine (8 to 16 mg) or equivalent.	Oral - as clinically indicated.	-	Optional
Antipyretic	Paracetamol/acetaminophen (500 mg to 1000 mg) or equivalent.	Oral - administer at least 30 minutes prior to study drug.	Yes	Optional
H_2-antagonist	Ranitidine (50 mg) or equivalent.	I.v. - start infusion 30 minutes prior to study drug.	Optional	-
Antiemetic	Ondansetron (16 mg) or equivalent.	I.v. - start infusion 30 minutes prior to study drug.	Optional	-
	Ondansetron (8 mg) or equivalent (long or short acting agents).	Oral - as clinically indicated.	-	Optional

i.v.=intravenous.
Note: Steroids may be used in case of severe reactions not controlled by other measures.

10.3 TREATMENT OF AUTO3 INFUSION-RELATED REACTIONS

Patients who experience infusion-related reactions (to pre-conditioning or AUTO3) that manifest as wheezing, flushing, hypoxemia, fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypo- or hypertension or other symptoms, should have the symptoms managed according to the recommendations provided in Table 17 or as per institutional practice. All NCI CTCAE Grade 3 or 4 infusion-related reactions should be reported within 24 hours to the Sponsor. If the event meets the criteria of an SAE, SAE reporting criteria in Section 12.3.5 should be followed.

Table 17: Guidelines for the Management of Infusion-related Reactions

NCI CTCAE Grade	Treatment/Intervention	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated.	No intervention indicated; Monitor patient as medically indicated until recovery from symptoms.	May consider diphenhydramine/chlorpheniramine 10 to 20 mg or equivalent and or paracetamol/acetaminophen 500 to 1000 mg if not instituted (see Table 16).
Grade 2 Moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment.	**Interrupt infusion** Start i.v. fluids; give diphenhydramine/chlorpheniramine 50 mg (or equivalent) i.v. and/or paracetamol/acetaminophen 500 to 1000 mg; consider bronchodilator therapy; may also consider corticosteroids if necessary; monitor patient closely until recovery from symptoms. Restart infusion if AUTO3 dose has not been fully administered. **Symptoms recur:** Stop and discontinue further infusion. The approximate amount of AUTO3 infused must be recorded on the eCRF.	Diphenhydramine/chlorpheniramine 10 to 20 mg or equivalent and/or paracetamol/acetaminophen 500 to 1000 mg if not instituted (see Table 16).
Grade 3 or 4 Severe reaction; **Grade 3**: prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates). **Grade 4**: life-threatening; pressor or ventilator support indicated	**Stop Infusion** Start i.v. saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10000 solution injected slowly for i.v. administration, and/or diphenhydramine/chlorpheniramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed, and other drugs as appropriate. Patients should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localised or generalised pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine or corticosteroids), as appropriate.	**Grade 3:** Discuss with Sponsor medical monitor about merits of completing AUTO3 infusion if full dose has not been administered. **Grade 4:** Permanently discontinue administration of any remaining AUTO3.
General	Appropriate personnel and appropriate resuscitation equipment should be available in or near the infusion room and a physician should be readily available during the infusion of study drug.	

CTCAE=Common Terminology Criteria for Adverse Events; eCRF=electronic Case Report Form; i.v.=intravenous; NCI=National Cancer Institute.

10.4 GRADING AND MANAGEMENT OF CYTOKINE RELEASE SYNDROME

Cytokine Release Syndrome is a recognised toxicity with CAR T cell therapies and, for some CAR T therapies, can be severe (Grade 3 or 4; 40% of patients with ALL and 20% of patients with DLBCL) (Kymriah (tisagenlecleucel) EU SmPC 2018, Kymriah US Prescribing Information 2018). Clinical symptoms indicative of CRS include culture negative fever, myalgia, nausea/vomiting, tachycardia, hypoxia, hypotension, headache, confusion, tremor, and delirium. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure, and DIC (Brudno and Kochenderfer 2016). Symptoms usually present within the first 1 to 2 weeks following infusion (Neelapu et al. 2018).

Some studies have suggested several possible risk factors for severe CRS, such as higher peak expansion level of CAR T, tumour burden, baseline high lactate dehydrogenase level, early onset CRS (within 3 days of infusion) and elevation of some cytokine levels after infusion (Hay et al. 2017, Locke et al. 2017, Santomasso et al. 2018).

Macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in some patients for whom CAR-mediated inflammatory responses continue to evolve. The clinical syndrome of MAS is characterised by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly (see Section 10.5). It is associated with biochemical abnormalities, such as high circulating levels of serum ferritin, soluble IL-2 receptor (sCD25), and triglycerides, together with a decrease of circulating natural killer cell activity. Other findings include variable levels of transaminases up to signs of acute liver failure and coagulopathy with findings consistent with DIC.

Following the first AUTO3 infusion, patients should be closely monitored for early signs and symptoms indicative of CRS, with clinical review and blood tests including C-reactive protein, serum ferritin levels, and clotting. Serum cytokines should be obtained periodically as indicated in the schedule of assessments. Clinical personnel should be trained in the diagnosis and management of CRS.

Grading for CRS is provided in Table 18, with recommendations regarding treatment provided in Table 19.

Table 18: Severity Grading of Cytokine Release Syndrome (ASTCT/ASBMT CRS Consensus Grading and CTCAE Version 5.0) (Lee et al. 2019)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever†	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or‡				
Hypoxia	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT/ASBMT=American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation; BiPAP=bi-level positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events.
Note: organ toxicities associated with CRS may be graded according to CTCAE Version 5.0 but they do not influence CRS grading.
† Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive anti-pyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
‡ CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS.
^ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in paediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Table 19: Management of Cytokine Release Syndrome

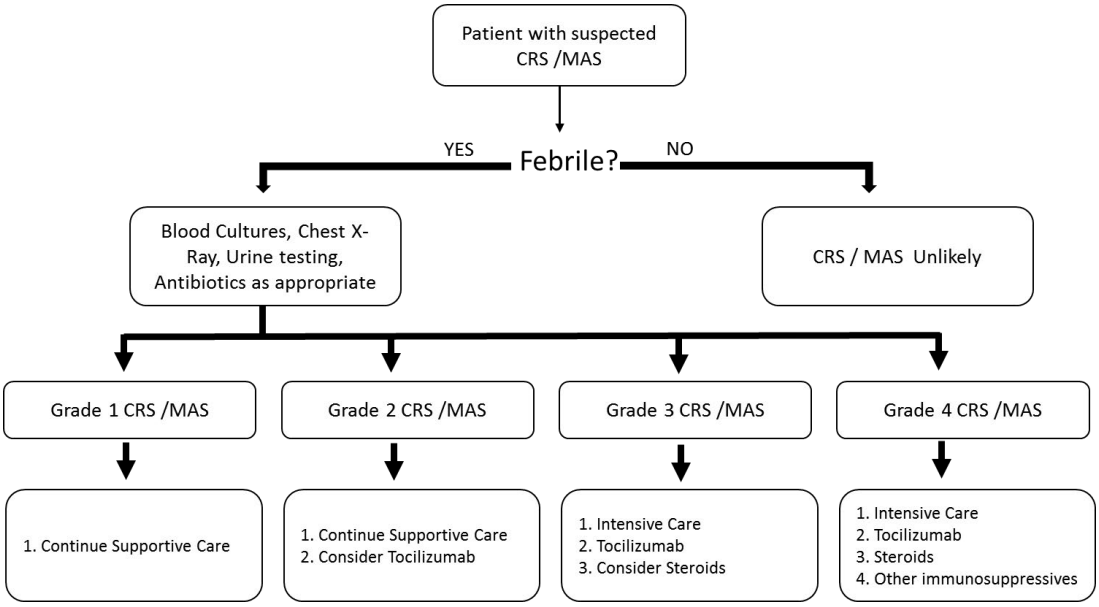
CRS Grade (CTCAE Version 5.0)	Treatment
Grade 1 Symptoms are not life-threatening and require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, and malaise or organ toxicity)	Supportive care per institutional standards including analgesics and antipyretics, assess and treat for neutropenic infections. Consider tocilizumab for persisting (>3 days) and/or refractory fever (persistent fever of ≥39°C despite antipyretics for 10 hours) (Lee et al. 2014, Neelapu et al. 2018).
Grade 2 Symptoms require and respond to moderate intervention	Supportive care including fluid substitution is recommended. Low-flow-oxygen (<40% fraction of inspired oxygen). Give tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention	Intensive care should be considered. Oxygen (flow ≥40% fraction of inspired oxygen). Vasopressors as needed (see Table 20). Treat with tocilizumab see Table 20. Add siltuximab as necessary if not previously administered. Add steroids if unresponsive within 24 hours. CRS associated with MAS or haemophagocytosis may also be treated with anakinra, an IL-1 receptor antagonist (Shah et al. 2017). Also, consider anti-TNF antibodies as clinically appropriate.

CRS Grade (CTCAE Version 5.0)	Treatment
Grade 4 Life-threatening symptoms	Intensive care. Treat with tocilizumab see Table 20. Add siltuximab as necessary if not previously administered. Treat with corticosteroids (see Table 20). CRS associated with MAS or haemophagocytosis may also be treated with anakinra, an IL-1 receptor antagonist (Shah et al. 2017). Consider alternative agents such as anti-TNF, and other agents as appropriate.
Grade 5 Death	Not applicable.

CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; IL=interleukin; MAS=macrophage activation syndrome; TNF=tumour necrosis factor.

An overview of CRS management is presented in Figure 4.

Figure 4: CRS Management Overview



CRS=cytokine release syndrome; MAS=macrophage activation syndrome.

Details of supportive medication and steroid doses are presented in Table 20.

Table 20: Pharmacologic Management of CRS

Drug	Indication	Dose
Vasopressor	Hypotension not responsive to fluid resuscitation alone. Vasopressor use according to local institutional practice. Noradrenaline/norepinephrine is the preferred first-line vasopressor (Brudno and Kochenderfer 2016). Recommended doses provided (Lee et al. 2014). Vasopressor should be used for at least 3 hours. Note: Vasopressin is not available in all countries.	Noradrenaline/norepinephrine monotherapy ≥0.2 µg/kg/minute Dopamine monotherapy ≥10 µg/kg/minute Adrenaline monotherapy ≥0.1 µg/kg/minute If on vasopressin: Vasopressin+noradrenaline/ norepinephrine equivalent of ≥10 µg/min*. If on a combination vasopressors (not vasopressin): Noradrenaline/norepinephrine equivalent of ≥20 µg/min*.

Drug	Indication	Dose
Anti-IL-6 therapy	Anti-IL-6 therapy may be given according to local institutional practice. Use of anti-IL-6 treatments is not currently believed to impair the efficacy of CAR T cell therapy, (Davila et al. 2014, Lee et al. 2015, Brudno and Kochenderfer 2016, Neelapu et al. 2018) Brudno and Kochenderfer (Brudno and Kochenderfer 2016) recommended the use of anti-IL-6 therapy (specifically tocilizumab) in the event of the following associated with CRS (CRS Grade ≥2 with associated conditions): • Left ventricular ejection fraction 40% by ECHO; • Creatinine >2.5-fold higher than the most recent level prior to CAR T cell infusion; • Norepinephrine requirement at a dose >2 mg/min for 48 hours since the first administration of norepinephrine, even if administration is not continuous; • SBP of 90 mm Hg that cannot be maintained with norepinephrine; • Oxygen requirement of fraction of inspired oxygen 50% or more for more than 2 hours continuously; • Dyspnoea that is severe enough to potentially require mechanical ventilation; • Activated PTT >2 × ULN; • Clinically-significant bleeding; • Creatine kinase >5 × ULN for longer than 2 days. Use of tocilizumab may also be considered for persistent fever of ≥39°C despite anti-pyretics for 10 hours, persistent/recurrent hypotension after initial fluid bolus, and initiation of oxygen supplementation (Lee et al. 2014, Neelapu et al. 2018). **Tocilizumab** Tocilizumab is approved in the US and Europe for the management of CRS patients (Actemra Prescribing Information 2018, RoActemra SmPC 2018). Refer to local prescribing information. Note: organ dysfunction secondary to CRS and cytopenias due to disease/chemotherapy will not constitute a contraindication to tocilizumab. **Siltuximab** Siltuximab is an alternative to tocilizumab (Grupp et al. 2013, Calabrese and Rose-John 2014, Maude et al. 2014, Teachey et al. 2018) and may be used according to local institutional guidance. Siltuximab has been approved to treat Castleman's disease (Neelapu et al. 2018, Siltuximab EU SmPC 2019, Siltuximab US Prescribing Information 2019). Siltuximab may be added if there is no response to tocilizumab±corticosteroids (Neelapu et al. 2018, Teachey et al. 2018).	Tocilizumab: The recommended dosing of tocilizumab for the treatment of CRS given as a 60-minute i.v. infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg (Maude et al. 2015). Tocilizumab can be given alone or in combination with corticosteroids. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients (Actemra Prescribing Information 2018, RoActemra SmPC 2018). Refer to local prescribing information and institutional guidance. Siltuximab: 11 mg/kg over 1 hour as a single i.v. infusion (Neelapu et al. 2018, Siltuximab EU SmPC 2019, Siltuximab US Prescribing Information 2019).

Drug	Indication	Dose
Corticosteroids	Corticosteroids should generally be avoided in patients who have received CAR T cell therapy, due to concerns of the effect on the T cells (Neelapu et al. 2018), though, some studies have shown a clinical response to CAR T therapy after high doses of methylprednisolone (Maude et al. 2015, Mueller et al. 2018). Corticosteroids are indicated in Grade 4 CRS and Grade 3 CRS refractory to anti-IL-6 therapy. Corticosteroids are also indicated in patients with NT (ICANS) Grade 2 and above (see Section 10.6). Patients with ICANS in the absence of CRS should receive corticosteroids prior to anti-IL-6 therapy (Riegler et al. 2019). Dosing and choice of corticosteroid should be tailored to the individual patient and according to local institutional guidance (if specified). Commonly used initial doses include methylprednisolone. For patients with suspected ICANS, dexamethasone may be more suitable, due to more efficient penetration of the blood brain barrier (Mitchell et al. 2005) (see Section 10.6). Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at the start of tapering or earlier, once sustained clinical improvement is observed. Prophylactic antibiotics or other antimicrobials as clinically appropriate. Rigorous control of blood pressure and electrolytes (particularly calcium and magnesium).	Methylprednisolone: 2 mg/kg i.v. every 12 hours weaned over 5 days. Dexamethasone: 10 mg i.v. every 6 hours (if refractory can increase to 20 mg every 6 hours) (Neelapu et al. 2018).
Anti-TNF therapy	**Infliximab** (anti-TNFα antibody) **Etanercept** (soluble TNFα receptor) These agents have also demonstrated efficacy in the setting of CRS, MAS and other syndromes (Prahalad et al. 2001, Flammiger et al. 2012, Gabay et al. 2014, Ruella et al. 2017)	Refer to local prescribing information.
Anti-IL-1 Therapy	**Anakinra** Uncontrolled MAS or haemophagocytosis may also be treated with anakinra, an IL-1 receptor antagonist (Brudno and Kochenderfer 2016, Shah et al. 2017, Liu and Zhao 2018).	100 mg by subcutaneous injection, to be repeated daily as clinically indicated.

CAR= chimeric antigen receptor; CRS=cytokine release syndrome; ECHO=echocardiogram; EU=European Union; ICANS=immune effector cell-associated neurotoxicity syndrome; IL=interleukin; i.v.=intravenous; MAS=macrophage activation syndrome; PTT=prothrombin time; SBP=systolic blood pressure; SmPC=Summary of Product Characteristics; TNF=tumour necrosis factor; ULN=upper limit of normal; US=United States.
* VASST Trial (Russel et al 2008) vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷10].

10.5 MANAGEMENT MACROPHAGE ACTIVATION SYNDROME (MAS)

Macrophage activation syndrome and HLH encompass a group of severe immunological disorders characterised by hyperactivation of macrophages and lymphocytes, proinflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure.

Haemophagocytic lymphohistiocytosis and/or MAS may occur in some patients for whom CAR-mediated inflammatory responses continue to evolve. The clinical syndrome of MAS is characterised by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly.

A patient might have HLH/MAS if they have a peak serum ferritin level of >10,000 ng/mL during the CRS phase of CAR T cell therapy and subsequently developed any two of the following (Neelapu et al. 2018):

- CTCAE Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels;
- CTCAE Grade ≥3 oliguria or increase in serum creatinine levels;
- CTCAE Grade ≥3 pulmonary oedema;
- Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry.

Haemophagocytic lymphohistiocytosis/MAS may be refractory to anti-IL-6 therapy and can be associated with high mortality if not treated promptly. Patients with suspected HLH/MAS should be treated with anti-IL-6 therapy and corticosteroids (Neelapu et al. 2018) (see Table 20). If the patient has no clinical or serological improvement within 48 hours, consider etoposide 75 to 100 mg/m^2 as appropriate (Jordan et al. 2011, Schram and Berliner 2015, Tamamyan et al. 2016). Intrathecal cytarabine can be considered in patients with HLH-associated NT (Neelapu et al. 2018).

Uncontrolled HLH/MAS may also be treated with anakinra, an IL-1 receptor antagonist (see Table 20) (Brudno and Kochenderfer 2016, Shah et al. 2017, Liu and Zhao 2018).

10.6 GRADING AND MANAGEMENT OF NEUROTOXICITY (ICANS)

Neurotoxicity has been seen in patients with leukaemia and lymphoma after treatment with CAR T cell therapy (Neelapu et al. 2018) and is now referred to as ICANS. The cause of NT is not well-understood, although it is generally reported to be fully reversible (Kymriah (tisagenlecleucel) EU SmPC 2018, Kymriah US Prescribing Information 2018). Enrichment of pro-inflammatory cytokines in the CNS, endothelial activation, and MAS have all been proposed as potential mechanisms (Karschnia et al. 2019). Transient neurological complications have also been reported with CD19 bispecific T cell engagers, suggesting that the target may have some relevance (Goebeler and Bargou 2016).

Although symptoms can vary, the early manifestations of ICANS are often tremor, dysgraphia, mild difficulty with expressive speech (especially naming objects), impaired attention, apraxia, and mild lethargy. Other symptoms can include confusion, depressed level of consciousness/encephalopathy, hallucinations, dysphasia, ataxia, apraxia, cranial nerve palsies, and seizures. Headache is a non-specific symptom, frequently occurring during fever or after chemotherapy; thus, headache alone is not a useful marker of ICANS. Expressive aphasia, on the other hand, appears to be a very specific symptom of ICANS (Santomasso et al. 2018).

In addition to more common NT symptoms such as encephalopathy, aphasia, delirium, tremor, and seizures; rare cases of rapid-onset and lethal diffuse cerebral oedema have occurred with some CAR T cell therapies (Gust et al. 2017, Locke et al. 2017, Gilbert 2018).

There appears to be no correlation between ICANS and CRS/MAS and both can occur together or separately (Santomasso et al. 2018), although ICANS occurs more frequently in the presence of severe CRS. There is also some suggestion that patients with a high disease burden prior to treatment, higher peak CAR T cell expansion and early and higher elevations of serum cytokines may have a higher risk of NT (Santomasso et al. 2018). Of note, patients can develop ICANS even after treatment of anti-IL-6 therapy, after the resolution of CRS.

Patients will be monitored closely after the first AUTO3 infusion for neurological signs and symptoms of NT. If NT is observed, a neurology opinion should be sought, MRI imaging performed, and the patient will receive supportive care (e.g. anti-convulsant therapy), as appropriate (see Table 23).

In general, as NT is transient and resolves spontaneously with no long-term sequelae, supportive care alone is sufficient in most patients. Steroids may be given for Grade 3 or 4 NT (see Table 23) or in the case of cerebral oedema or generalised seizures, but otherwise treatment with steroids should be avoided as this may be deleterious to the persistence of AUTO3.

Neurotoxicity may also be caused by FLU but usually at higher doses than those being administered in this protocol (Helton et al. 2013). Symptoms of FLU including objective weakness, agitation, confusion, seizures, visual disturbances, optic neuritis, optic neuropathy, blindness, and coma have been reported in patients with chronic lymphocytic leukaemia treated with multiple cycles of FLU.

Neurotoxicity may also be associated with prior methotrexate treatment (either high dose or intrathecal) (Inaba et al. 2008, Bhojwani et al. 2014). Although neurological toxicities associated with methotrexate are usually acute, radiological abnormalities may persist (Bhojwani et al. 2014).

Please see Table 21 for grading of NT as per the ASTCT/ASBMT guidelines for ICANS (Lee et al. 2019).

Table 21: Assessment & Grading of ICANS

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
ICE Score^ for Adults (see Table 22)	7 to 9	3 to 6	0 to 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness*	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure, focal or generalised, that resolves rapidly; or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 minutes); or Repetitive clinical or electrical seizures without return to baseline in between
Motor weakness§	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

	Grade 1	Grade 2	Grade 3	Grade 4
Raised ICP/cerebral oedema	N/A	N/A	Focal/local oedema on neuroimaging[#]	Decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad; or signs of diffuse cerebral oedema on neuroimaging

ASTCT/ASBMT=American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation; CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable.
Adapted from Lee 2019, ASTCT/ASBMT ICANS Consensus (Lee et al. 2019).
ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema) not attributable to any other cause.
^ A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia; however, a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable.
* Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication).
§ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE Version 5.0, but they do not influence ICANS grading.
# Intracranial haemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE Version 5.0.

Table 22: Immune Effector Cell-associated Encephalopathy (ICE) Scale

Orientation: orientation to year, month, city, hospital	4 points
Following commands: ability to follow simple commands (e.g. "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Naming: ability to name 3 objects (e.g. point to clock, pen, button)	3 points
Writing: ability to write a standard sentence (e.g. "Our national bird is the bald eagle")	1 point
Attention: ability to count backwards from 100 by 10	1 point
Scoring 10, no impairment; 7 to 9, Grade 1 ICANS; 3 to 6, Grade 2 ICANS; 0 to 2, Grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment.	

ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy.

Patients may be managed as per the suggested guidelines below (Table 23) but may also be managed as per institutional management guidelines.

Table 23: Management of ICANS

Grade 1	Vigilant supportive care; aspiration precautions; i.v. hydration. Withhold oral intake of food, medicines and fluids, and assess swallowing. Convert all oral medications and/or nutrition to i.v. if swallowing is impaired. Avoid medications that cause CNS depression. Low doses of lorazepam (0.25 to 0.5 mg i.v. every 8 hours) or haloperidol (0.5 mg i.v. every 6 hours) can be used, with careful monitoring, for agitated patients. Neurology consultation. Fundoscopic exam to assess for papilledema. MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI of the spine if the patient has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible. Consider daily 30 minute EEG until toxicity symptoms resolve; if no seizures are detected on EEG. Consider levetiracetam 750 mg every 12 hours (oral or i.v.) for a month for seizure prophylaxis. If EEG shows non-convulsive status epilepticus, treat as per the algorithm in Table 24. Consider anti-IL-6 therapy if NT is associated with concurrent CRS (see Section 10.4). **Worsening**: treat as ≥Grade 2.
Grade 2	Supportive care and neurological work-up as indicated for Grade 1. Anti-IL-6 therapy if associated with concurrent CRS (see Section 10.4). Dexamethasone 10 mg i.v. every 6 hours or methylprednisolone 1 mg/kg i.v. every 12 hours if refractory to anti-IL-6 therapy, or for NT without concurrent CRS. Consider transferring the patient to ICU if NT is associated with Grade ≥2 CRS. **Worsening**: treat as Grade 3 to 4.
Grade 3 neurologic toxicities (with the exception of headaches, that last continuously for 24 hours or longer)	Supportive care and neurological work-up as indicated for Grade 1. ICU transfer is recommended. Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 2 NT and if not administered previously. Dexamethasone 10 mg i.v. every 6 hours or methylprednisolone 1 mg/kg i.v. every 12 hours if refractory to anti-IL-6 therapy, or for NT without concurrent CRS; continue corticosteroids until improvement to Grade 1 NT and then taper (see Table 20.Stage 1 or 2 papilledema with CSF opening pressure <20 mmHg should be treated as per the algorithm in Table 25. Consider repeat neuroimaging (CT or MRI) every 2 to 3 days if patient has persistent Grade ≥3 NT.

Grade 4 neurologic toxicity of any duration **Any generalised seizures**	Supportive care and neurological work-up as outlined for Grade 1 NT. ICU monitoring; consider mechanical ventilation for airway protection. Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 NT. High-dose corticosteroids continued until improvement to Grade 1 NT and then taper; for example, methylprednisolone i.v. 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days (see Table 20). For convulsive status epilepticus, treat as per the algorithm in Table 24. Stage ≥3 papilledema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per the algorithm in Table 25. **Worsening:** May consider use of lymphodepleting drugs such as CY (Garfall et al. 2015) or other drugs (Klinger et al. 2016) if unresponsive to standard immunosuppressive therapies.

Adapted from (Neelapu et al. 2018).
CRS=cytokine release syndrome; CNS=central nervous system; CSF=cerebrospinal fluid; CT=computerised tomography; CY=cyclophosphamide; EEG=electroencephalogram; ICU=intensive-care unit; IL=interleukin; i.v.=intravenous; MRI=magnetic resonance imaging.

Table 24: Recommendations for the Management of Status Epilepticus After CAR T Cell Therapy

Event	Management
General	Patients should be managed according to local institutional practice and with the consultation, or management, of a neurologist.
Non-convulsive status epilepticus	Assess airway, breathing, and circulation; check blood glucose. Lorazepam 0.5 mg i.v., with additional 0.5 mg i.v. every 5 minutes, as needed, up to a total of 2 mg to control electrographical seizures. Levetiracetam 500 mg i.v. bolus, as well as maintenance doses. If seizures persist, transfer to ICU and treat with phenobarbital loading dose of 60 mg i.v. Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg i.v. every 8 hours for three doses; levetiracetam 1000 mg i.v. every 12 hours; phenobarbital 30 mg i.v. every 12 hours.
Convulsive status epilepticus	Assess airway, breathing, and circulation; check blood glucose. Transfer to ICU. Lorazepam 2 mg i.v., with additional 2 mg i.v. to a total of 4 mg to control seizures. Levetiracetam 500 mg i.v. bolus, as well as maintenance doses (as age appropriate). If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg i.v. Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg i.v. every 8 hours for three doses; levetiracetam 1000 mg i.v. every 12 hours; phenobarbital 1 to 3 mg/kg i.v. every 12 hours. Continuous electroencephalogram monitoring should be performed, if seizures are refractory to treatment.

Adapted from (Neelapu et al. 2018).
CAR=chimeric antigen receptor; ICU=intensive-care unit; i.v.=intravenous.
All indicated doses of medication are for adult patients. Please check local prescribing information.

Table 25: Recommendation for Management of Raised Intracranial Pressure After CAR T Cell Therapy

Condition	Management
Stage 1 or 2 papilledema* with CSF opening pressure of <20 mmHg without cerebral oedema	Acetazolamide 1000 mg i.v., followed by 250 to 1000 mg i.v. every 12 hours (adjust dose based on renal function and acid–base balance, monitored 1 to 2 times daily).
Stage 3, 4, or 5 papilledema*, with any sign of cerebral oedema on imaging studies, or a CSF opening pressure of ≥20 mmHg	Use high dose corticosteroids with methylprednisolone i.v. 1 g/day (see Table 20). Elevate head end of the patient's bed to an angle of 30 degrees. Hyperventilation to achieve target partial pressure of arterial carbon dioxide of 28 to 30 mmHg but maintained for no longer than 24 hours. Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below): • Mannitol: initial dose 0.5 to 1 g/kg; maintenance at 0.25 to 1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40. • Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50 to 75 mL/hour while monitoring electrolytes every 4 hours, and withhold infusion if serum sodium levels reach ≥155 mEq/L. • For patients with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 minutes, if needed. If patient has Ommaya reservoir, drain CSF to target opening pressure of <20 mmHg. Consider neurosurgery consultation and i.v. anaesthetics for burst-suppression pattern on electroencephalography. Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension.

Adapted from (Neelapu et al. 2018).
CAR=chimeric antigen receptor; CSF=cerebrospinal fluid; CT=computerised tomography; i.v.=intravenous.
*papilledema grading should be performed according to the modified Frisén scale (Frisen 1982).

10.7 MANAGEMENT OF TUMOUR LYSIS SYNDROME

Treatment with CAR T cells, such as AUTO3, can lead to rapid destruction of malignant B cells, which can be associated with a release of intracellular ions and metabolic by-products into the systemic circulation and can thus result in signs and symptoms indicative of TLS. Clinically, TLS can be characterised by rapid development of hyperuricemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia, and potentially acute renal failure.

Early recognition and monitoring of signs and symptoms of patients at risk for TLS, including identification of abnormal clinical and laboratory values, can lead to successful prevention of the serious clinical complications of the condition. Supportive care should be initiated according to the institutional standards and at the Investigator's discretion.

Management of TLS, including dehydration and management of abnormal laboratory test results such as hyperkalaemia, hyperuricemia, and hypocalcaemia, is highly recommended. It is also recommended that high-risk patients, i.e. those with a high tumour burden, be treated

prophylactically in accordance with local standards (e.g. rehydration, diuretics, allopurinol, rasburicase, and other medication to increase urate excretion).

10.8 HYPOGAMMAGLOBULINEMIA AND B CELL APLASIA

Hypogammaglobulinaemia has been seen as a consequence of depletion of normal B cells by CAR T therapy (Doan and Pulsipher 2018). CAR T cell therapy targeting antigens found on the surface of B cells not only kills cancerous B cells but also normal B cells. Therefore, B cell aplasia (low numbers of B cells or absent B cells) is an expected result of successful CD19-specific CAR T cell treatment and has served as a useful indicator of ongoing CAR T cell activity. This effect results in reduced ability to manufacture the antibodies that protect against infection. Intravenous or subcutaneous Ig replacement therapy may be given with the aim of preventing infection. However, the degree and duration of this is likely to depend on the persistence of CAR T cells in the body and could last for months to years. At worst, the clinical consequences of therapeutic B cell elimination will resemble X-linked agammaglobulinaemia and patients with this disorder have a normal life expectancy when treated with regular i.v. Ig replacement. Immunoglobulin levels will be monitored regularly as per the Schedule of Assessments (Table 1 and Table 2) and patients with severe hypogammaglobulinaemia (serum IgG level is <4 g/L) persisting longer than 6 months are recommended to be treated with i.v. Ig administration until recovery of B cells and normal IgM levels, or lifelong if this does not occur.

Management of Hypogammaglobulinaemia Associated with CAR T Therapy will be according to local institutional practice.

10.9 INFECTIOUS DISEASES

Prophylactic anti-bacterial treatment, such as trimethoprim-sulfamethoxazole (or alternative drugs), for pneumocystis prophylaxis and prophylactic antivirals, such as acyclovir or valacyclovir, for herpes virus prophylaxis may be initiated prior to pre-conditioning chemotherapy and continued until lymphopenias have resolved or as clinically indicated. All patients with fevers and neutropenia should have blood cultures drawn and assessment for broad-spectrum antibiotics done per institutional practice.

10.10 MANAGEMENT OF IMMUNE RELATED ADVERSE EVENTS DUE TO ON-TARGET BUT OFF-TUMOUR TOXICITY

Though it is unlikely that AUTO3 will cause immune-related AEs (irAEs) due to on-target but off-tumour toxicity, the patients will be closely monitored for signs and symptoms indicative of irAEs, which may allow for an early recognition of these events. Special attention will be paid to vital organs and for irAEs of any grade involving vital organs (e.g. lung, brain, and eyes), more aggressive monitoring and rapid institution of appropriate supportive care including systemic steroids, should be administered. In case of severe irAE, not successfully managed by general supportive care, treatment with steroids and other agents may be considered.

10.11 MANAGEMENT OF PEMBROLIZUMAB RELATED IMMUNE TOXICITY

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic aetiology are outlined below. Where appropriate, these guidelines include the use of oral or i.v. corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. Attempts should be made to rule out other causes such as underlying disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines in this section are intended to be applied when the Investigator determines the events to be related to pembrolizumab. The SmPC/USPI for pembrolizumab should also be consulted for guidance on managing these associated events.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

10.11.1 Pneumonitis and Pulmonary AE

Pulmonary AEs, including radiographic changes (e.g. focal ground glass opacities and patchy infiltrates) indicative of drug-related pneumonitis, have been observed in patients receiving immuno-oncology agents. These pulmonary AEs were either asymptomatic or associated with symptoms such as dyspnoea, cough, or fever. The initial occurrence of pulmonary AEs may be as early as after a single dose of pembrolizumab or delayed after prolonged therapy. Early recognition and treatment of pneumonitis is critical to its management. Patients should be advised to seek medical evaluation promptly if they develop new-onset dyspnoea, cough, or fever or if they have worsening of these baseline symptoms.

Table 26: Management and Follow-up of Pulmonary Adverse Events

Management and Follow-up of Pulmonary AEs	
Grade 1	Monitor for symptoms every 2 to 3 days; consider pulmonary and infectious disease consult; re-image every 3 weeks. **Worsening:** treat as ≥Grade 2.
Grade 2	Monitor symptoms daily; re-image every 1 to 3 days; pulmonary and infectious disease consultation; consider bronchoscopy and lung biopsy; consider hospitalisation. **Immediately:** start 1.0 mg/kg/day methylprednisolone i.v. or oral equivalent; prophylactic antibiotics **Persistence for 2 weeks or worsening:** treat as Grade 3 to 4; **Improvement to ≤Grade 1 or baseline:** taper steroids over at least 1 month.
Grade 3 to 4	Hospitalise; pulmonary and infectious disease consultation; consider bronchoscopy and lung biopsy. **Immediately:** 2 to 4 mg/kg/day methylprednisolone or i.v. equivalent; add prophylactic antibiotics; **Persistence for 2 days or worsening:** add immunosuppression (e.g. infliximab, CY, i.v. Ig, or mycophenolate mofetil) **Improvement to ≤Grade 2:** taper steroids over at least 6 weeks.

Management and Follow-up of Pulmonary AEs	
General	Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids should be considered.

AE=adverse event; CY=cyclophosphamide; Ig=immunoglobulin; i.v.=intravenous.

10.11.2 Diarrhoea/Colitis

- Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood, or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
- All patients who experience diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.

Table 27: Management and Follow-up of Immune-related GI AEs

Management and Follow-up of Immune-related GI AEs	
Grade 1	Symptomatic treatment per institutional standards. Close monitoring; instruct patient to report worsening immediately and treat as Grade ≥2.
Grade 2	**≤5 days:** Symptomatic treatment per institutional standards. **>5 days or recurrence:** 0.5 to 1.0 mg/kg/d methylprednisolone; consider prophylactic antibiotics. **Persistence or worsening despite steroids >3 days:** treat as Grade 3/4. **Improvement to ≤Grade 1:** taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study therapy per protocol.
Grade 3 to 4	**Immediately:** 1.0 to 2.0 mg/kg/d methylprednisolone i.v.; consider prophylactic antibiotics and lower endoscopy. **Persistence >3 days or recurrence:** add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis). **Improvement to ≤Grade 2 within ≤3 days:** taper steroids over at least 1 month.
General	The oral corticosteroid equivalent of the recommended i.v. dose may be considered for ambulatory patients; the lower bioavailability of oral corticosteroids needs to be considered. Clinical caution should be exercised, for patients receiving concomitant medications of corticosteroids, non-steroidal anti-inflammatory drugs (NSAID), or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in patients with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation.

AE=adverse event; GI=gastrointestinal; Ig=immunoglobulin; i.v.=intravenous; NSAIDs=non-steroidal anti-inflammatory drugs.

10.11.3 Type 1 diabetes mellitus

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥Grade 3 Hyperglycaemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

For **type 1 diabetes mellitus** or **Grade 3 to 4 hyperglycaemia**:

- Insulin replacement therapy is recommended for type 1 diabetes mellitus and for Grade 3 to 4 hyperglycaemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.

10.11.4 Hypophysitis

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3 to 4** events, treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

10.11.5 Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Hyperthyroidism

- **Grade 2** hyperthyroidism events (and **Grade 2 to 4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3 to 4** hyperthyroidism
  - Treat with an initial dose of i.v. corticosteroid followed by oral corticosteroids. When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

10.11.6 Hepatic Events

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly). Treat with i.v. or oral corticosteroids.
- For **Grade 3 to 4** events, treat with i.v. corticosteroids for 24 to 48 hours.
- When symptoms improve to **Grade 1 or less**, a steroid taper should be started and continued over no less than 4 weeks.

10.11.7 Renal Failure or Nephritis

- For **Grade 2** events, treat with oral corticosteroids.

- For **Grade 3 to 4** events, treat with systemic corticosteroids.
- When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks.

10.11.8 Rash and Pruritus

- For **Grade 2** events, treat symptomatically and with oral corticosteroids.
- For **Grade 3 to 4** events, treat with systemic corticosteroids. consult dermatologist; consider skin biopsy.
- When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks.

10.11.9 Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 28 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

Table 28: Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 hours	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: i.v. fluids Antihistamines NSAIDs Paracetamol/acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping pembrolizumab infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hour to 50 mL/hour). Otherwise dosing will be held until symptoms resolve and the patient should be pre-medicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be pre-medicated 1.5 hours (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine/ chlorpheniramine 50 mg orally (or equivalent dose of antihistamine). Paracetamol/ acetaminophen 500 to 1000 mg orally (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: i.v. fluids Antihistamines NSAIDs Paracetamol/acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalisation may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing.
GENERAL	Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.	

CTCAE=Common Terminology Criteria for Adverse Events; i.v.=intravenous; NCI=National Cancer Institute; NSAIDs=non-steroidal anti-inflammatory drugs.

11 CONCOMITANT MEDICATIONS AND THERAPIES

All concomitant medications taken or received by the patient from Day -6 until 75 days post-AUTO3 infusion must be recorded along with the reason for use and should include:

- Dates of administration, including start and end dates.
- Dosage information including dose and frequency.

Only concomitant medication related to AEs attributed to AUTO3 or pembrolizumab treatment will be recorded from Day 75 post-AUTO3 infusion onwards. Concomitant medication may be given as medically indicated. Details of the concomitant medication/treatment given must be recorded in the patient's medical records and details entered into the eCRF. Standard drugs required by the patient may be administered alongside the trial protocol.

All safety management guidelines are only recommendations and deviations from this scheme are allowed according to the Investigator's judgement and local institutional practice.

11.1 BRIDGING THERAPY

Patients may receive bridging therapy while the product is being manufactured. The dates of bridging therapy, the chemotherapy agents and the doses given must be recorded in the eCRF. Additionally, the intent of bridging therapy, such as prevention of disease progression or induction of response in a rapidly progressing disease, should be documented in the eCRF.

Cytotoxic chemotherapies should be stopped 2 weeks prior to AUTO3 infusion. Other therapies should also have an adequate washout as indicated in exclusion criterion 17. Patients should have a baseline PET/CT after the bridging chemotherapy is given and prior to starting pre-conditioning.

11.2 ALLOWED CONCOMITANT MEDICATIONS/THERAPIES

Palliative radiotherapy: Palliative radiotherapy may be given concomitantly as clinically appropriate.

Other permitted therapies: The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Anti-microbials including antivirals and supportive therapy as required to prevent infections.
- Colony stimulating factors (use granulocyte-macrophage colony-stimulating factors [GM-CSF] with caution up to 3 weeks after AUTO3 infusion, due to the potential to worsen CRS symptoms. Granulocyte-colony stimulating factor (G-CSF) would be the preferred myeloid growth factor over GM-CSF, if medically indicated. The effects of G-CSF are unknown and can be used at the physician's discretion).
- Erythropoietin, and transfusion of platelets and red cells.

Pre- and post-AUTO3 infusion supportive therapies:

Please refer to Section 10.2.

11.3 PROHIBITED AND CAUTIONARY THERAPIES

Herbal, homeopathic agents or very high dose vitamins and mineral supplements: No herbal, homeopathic agents or very high dose vitamin and mineral supplements will be allowed between Day -10 and Day 56 following AUTO3 infusion, unless recommended by the Principal Investigator.

Corticosteroids and immunosuppressant (except for managing treatment related toxicity): Patients should not be receiving corticosteroids at doses of >5 mg prednisolone or equivalent within 7 days of leukapheresis and 72 hours prior to the time of AUTO3 infusion. The use of immunosuppressants such as high dose corticosteroids should be avoided where possible, as these are likely to influence the efficacy and possibly safety of AUTO3. As per the exclusion criteria, immunosuppressants should be stopped ≥2 weeks prior to leukapheresis or AUTO3 infusion. Corticosteroids should also be avoided post-AUTO3 infusion if possible, although it is recognised that their use may be required in the context of development of CRS or infusion reactions. Physicians may use any medication as clinically appropriate and necessary to manage emerging AEs. The use of other immunosuppressants should be discussed with the Sponsor's Medical Monitor.

Anti-cancer therapies: In general, patients should not receive other anti-cancer therapy or any other investigational anti-cancer drugs after administration of AUTO3.Administration of other systemic anti-cancer therapy at any time will be considered an indicator of treatment failure (progressive disease). However, palliative radiotherapy for symptom control can be administered without necessarily indicating progressive disease. Patients who have been administered AUTO3 and subsequently require alternative anti-cancer therapy will complete the End of Study visit and roll on to a follow-up protocol.

Investigators can use any medication based on their clinical judgement and local institutional practice to optimise patient's safety. All medications should be recorded on the eCRF.

11.4 OVER-DOSAGE

There is currently no experience of overdose of AUTO3 as no clinical studies have been performed to date. There is no specific treatment for an overdose of AUTO3. In the event of overdose, any adverse reactions should be treated symptomatically. In the event of unmanageable toxicity, steroids may be used to deplete AUTO3.

AUTO3 cells will be provided in patient specific dose aliquots and will be administered by trained staff in a hospital setting; therefore, the chance of overdose is unlikely.

11.5 DIETARY AND LIFESTYLE RESTRICTIONS

No dietary restrictions are recommended. A normal balanced diet is recommended; the patient may continue his/her normal diet as appropriate.

Donating blood products and organs

Patients should not donate blood, organs, tissue or cells to others after receiving AUTO3.

12 SAFETY AND PHARMACOVIGILANCE

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

12.1 DEFINITIONS

12.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

12.1.2 Definition of an Adverse Reaction

An adverse reaction is any untoward and unintended response to a medicinal product that is related to any dose administered. A causal relationship between a medicinal product and an AE is at least a reasonable possibility, e.g. the relationship cannot be ruled out.

An unexpected adverse reaction is an adverse reaction in which the nature or severity of which is not consistent with the Reference Safety Information section outlined in the IB for AUTO3 and SmPC for pembrolizumab.

12.1.3 Definition of a Serious Adverse Event

A SAE is defined as an AE that meets any of the following criteria:

- **Results in death** (death due to disease progression will not be considered as an SAE).
- **Life-threatening** (the term 'life-threatening' refers to an event for which the patient was at risk of death at the time of the event. It does not include any AE that, had it occurred in a more severe form, might have caused death).
- **Requires in-patient hospitalisation or prolonged existing hospitalisation.**
- **Results in persistent or significant disability/incapacity.**
- **Congenital anomaly/birth defect.**
- **Medically significant** (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above).

If the event was initially non-serious, the onset of the SAE should be considered the time when the AE met the seriousness criteria. Resolution of the SAE should also be considered when the event is either a non-serious event or has resolved.

Serious adverse events must be reported by the Investigator to the Sponsor within 24 hours of being made aware of their existence (see Section 12.3.5 for reporting instructions).

Protocol-Specific SAEs are as follows:

- Grade 4 CRS and NT.
- Any new primary cancers.
- Significant cardiac dysfunction such as Grade 3 or higher decrease in left ventricular ejection fraction.
- Grade 4 non-haematological laboratory abnormalities (not disease related) when considered clinically significant.

Serious adverse events must be reported by the Investigator to the Sponsor within 24 hours of being made aware of their existence (see Section 12.3.5 for reporting instructions).

Events NOT considered as SAEs:

- A procedure requiring hospitalisation for protocol/disease-related investigations (e.g. surgery, scans, endoscopy, sampling for laboratory tests, BM sampling). However, hospitalisation or prolonged hospitalisation for a complication of such procedures remains a reportable SAE.
- Hospitalisation for administration of pre-conditioning chemotherapy or conducting study procedures.
- Routine treatment or monitoring of the indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as a routine treatment of the studied indication. However, hospitalisation or prolonged hospitalisation for a complication of such transfusion remains a reportable SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.
- Hospitalisation of patients in the Phase I – expansion cohort being treated in the outpatient/ambulatory setting, where the Investigator feels the patient should be monitored as an inpatient for technical, practical, or social reasons (such as the lack of an adequate caregiver), in absence of AEs that meet the seriousness criteria (Section 12.1.3).
- Hospitalisations not intended to treat an acute illness or AE (e.g. social reasons such as pending placement in a long-term care facility). A procedure that is planned (i.e. planned prior to starting of treatment on study), which must be documented in the source document and eCRF. Hospitalisation or prolonged hospitalisation for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication. Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.
- An event that is part of the natural course of the disease under study (e.g. disease progression or hospitalisation due to disease progression, pain control, stabilisation of fractures) does not need to be reported as an SAE. Death due to the disease under study is to be recorded on the Death eCRF page. However, if progression of the underlying disease is greater than that which would normally be expected for the patient, or if the Investigator

considers that there was a causal relationship between treatment with study medication(s) and/or the disease progression, then this must be reported as an SAE.

12.1.4 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is any suspected adverse reaction related to the study treatment that is both unexpected and serious (see Section 12.3.6).

12.1.5 Adverse Events of Special Interest

The following are AEs of special interest.

- Grade 3 or 4 AUTO3 infusion related reaction.
- Grade 3 to 5 CRS.
- Grade 3 to 5 NT (including depressed level of consciousness, dysphagia, ataxia, seizures, and cerebral oedema).
- Any new malignancies (regardless of causality) including details of any applicable subtype and associated treatment
- New incidence or exacerbation of a pre-existing Neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of a hematologic disorder

Adverse events of special interest will be reported on an AESI/SAE form to the Sponsor within 24 hours of becoming aware of the event. Events can be both an AESI and a SAE (Sections 12.3.5 and 12.3.7).

12.1.6 Disease Progression

Due to the nature of the disease under investigation, disease progression is an anticipated occurrence in many patients, due to the nature and prognosis of the disease. Disease progression is therefore not considered an AE, unless the disease progression is greater than that which would normally be expected for that patient, or if the Investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE, due to the medical significance of the event.

12.2 ASSESSMENT OF ADVERSE EVENTS

Adverse events will be elicited at each study visit as indicated in Schedule of Assessments and as clinically necessary. Patients will be instructed to report any AEs occurring between study visits to the study site. Adverse events will be assessed by the Investigator, or appropriately qualified designee, for severity, relationship to study treatment, action taken, outcome and whether the event meets criteria as an SAE according to the guidelines presented in Section 12.1.3.

12.2.1 Severity of Adverse Events

The severity of AEs will be graded according to the NCI CTCAE (Version 5.0).

Adverse events that are not defined in the NCI CTCAE should be evaluated for severity according to the following scale:

Table 29: Severity Grading of AEs Not Listed on the NCI CTCAE Grading System

Grade	Severity	
1	Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
2	Moderate	Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible.
4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable.
5	Fatal	Death as a result of this AE.

AE=adverse event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.3.

Grade 3 or 4 severity does not necessarily imply seriousness. Due to the nature of the patient's disease and treatment, Grade 3 and 4 cytopenia (neutropenia, thrombocytopenia and anaemia) are common and are not usually considered medically significant in this context. For other events, there should be a low threshold in considering a Grade 3, and particularly a Grade 4 event as serious.

12.2.2 Relationship of AEs to Treatment

The Investigator must determine the relationship between the administration of the study drug and the occurrence of an AE/SAE as defined below:

Relationship assessments classified as "Not Related" to study treatment:

Not Related: The AE is not related to the investigational medicinal product. The patient either did not receive the investigational product or the event is related to aetiology other than the investigational product (the alternative aetiology must be documented in the study patient's medical record).

Unlikely Related: The AE is doubtfully related to the investigational product.

The event is not clearly related to an identified aetiology other than the investigational product; but there is no plausible mechanism for the event to be related to the investigational product and/or there is no clear association between the event and the administration of the investigational product.

Relationship assessments classified as "Related" to study treatment:

Possibly Related: The AE may reasonably be related to the investigational product.

Probably Related: The AE is likely to be related to the investigational product.

There is an association between the event and the administration of the investigational product, there is a plausible mechanism for the event to be related to the investigational product, the event is less likely to be explained by known characteristics of the patient's clinical status, and an alternative aetiology is not apparent.

Definitely Related: The AE is clearly related to the investigational product.

If an event is assessed as related to a drug other than the investigational product, which has not been provided by the Sponsor, the name of the manufacturer must be provided when reporting the event.

12.3 REPORTING PROCEDURES

12.3.1 All Adverse Events

The AE event term recorded in the eCRF, when possible and appropriate, should be the 'medical diagnosis' using the most appropriate medical term. If a diagnosis is not known, then the signs and symptoms should be included. This can be updated later, when a diagnosis has been made.

Signs and symptoms, or additional known associated events (e.g. febrile neutropenia with fever and neutropenia) do not need to be reported as additional event terms and should be described in the narrative. Signs, symptoms or other events, not normally associated with the reported event, should be added as additional events (e.g. febrile neutropenia and liver function abnormal).

All measures required to manage an AE must be recorded in the patient's medical notes and reported accordingly in the eCRF.

Death is an outcome and should not be considered an AE, unless no other appropriate diagnosis can be made. This should be updated when a cause of death has been established.

In principle all AEs, including SAEs should be collected from the time that the patient consents to the study. However, due to the long period between consent and treatment with AUTO3, any AEs/SAEs related to bridging chemotherapy that are not associated with study procedures do not require reporting as study AEs/SAEs. Any significant events should be added to the patient's medical history. All AEs/SAEs related to study procedures (leukapheresis, bone marrow assessments etc) should be reported.

All AEs/SAEs are to be recorded from admission for pre-conditioning chemotherapy (Day -7). Due to the patient's disease state and expected effect of chemotherapy on laboratory values, not all laboratory value abnormalities will be considered as AEs (see Section 12.3.2). Changes to laboratory values are better assessed through individual laboratory measurements.

The reporting period for all AEs is described in Table 30.

Table 30: Reporting Period for All AEs

From: ICF signature **Until**: Day -6	**From**: Day -6 **Until**: Day 75 post-AUTO3 infusion	**From**: Day 75 post-AUTO3 infusion **Until**: End of study/patient withdrawal OR, when patient initiates a new treatment for their disease
• AEs/SAEs related to study procedures (leukapheresis, bone marrow assessments, lumbar punctures etc). Note: AEs/SAEs associated with bridging therapy prior to admission for conditioning chemotherapy, are not associated with study procedures and therefore do not need to be reported as AEs in this study. If significant, these should be included in the patient's medical history.	• All AEs. • All SAEs.	• All AEs (regardless of grade) considered related to AUTO3. • All AEs of special interest (regardless of relationship to AUTO3) (Section 12.3.6). • All AEs related to study procedures (bone marrow assessments, lumbar punctures etc) regardless of relationship to AUTO3. All SAEs (regardless of relationship to AUTO3). If a patient starts a new treatment for disease progression or undergoes a stem cell transplant: • Only AEs (serious and non-serious) that are considered related to AUTO3 to be reported.

AE=adverse event; ICF=informed consent form; SAE=serious adverse event.

The Investigator should follow each AE until either:

- The AE has resolved to baseline;
- The AE is assessed as stable by the Investigator;
- Patient is lost to follow-up;
- Patient withdraws consent;
- Death;
- Study completion (or disease progression and patient withdrawn).

If a drug-related AE and/or any SAE is ongoing at the time of study completion, the event will be followed until resolution, is assessed as stable by the Investigator, or one of the following apply:

- Death;
- Withdrawal of consent;
- Start of new treatment/stem cell transplant; or
- Patient lost to follow-up.

Patients who enter a long-term safety study will have their events considered as continuing at the completion of this study, and the event will be followed up, as applicable, in the long-term safety study.

12.3.2 Adverse Events Associated with Laboratory Values

Anaemia, neutropenia, and thrombocytopenia requiring blood product support are anticipated (due to disease and pre-conditioning) and are therefore not considered AEs, unless they persist beyond Day 30 after CAR T cell infusion or are considered clinically significant and/or require advanced intervention above blood product and granulocyte-colony stimulating factor support.

Grade 1 to 2 laboratory abnormalities, at any time point, are extremely frequent in this patient population and do not need to be considered AEs unless they are felt to be clinically significant by the Investigator.

Whenever possible, AEs associated with laboratory values, should have these values included in the eCRF (e.g. reporting of AEs such as febrile neutropenia should be associated with temperature reading entry in vitals and absolute neutrophil counts in laboratory sections of the eCRF).

It should be noted that a single laboratory measurement may not have any clinical significance and may need to be taken in the context of other observations.

Abnormal laboratory values may be deemed clinically significant by the Investigator if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline, in the context of the patient's disease state and recent chemotherapy and/or CAR T cell therapy.
- The abnormality is of a degree that requires additional active management (e.g. closer observation, more frequent follow-up assessments, or further diagnostic investigation).
- Prolonged Grade 4 cytopenia lasting more than 60 days or those considered medically significant or requiring significant management in addition to transfusions and growth factor support (e.g. stem cell top up or transplant) should be reported as SAEs.

If the abnormal laboratory value(s) indicate a specific medical condition or diagnosis, then this medical condition, rather than the laboratory result, should be used as the AE reported term (see Section 12.3.1).

12.3.3 Adverse Events Associated with Cytokine Release Syndrome

As CRS can present with multiple signs and symptoms, it is important to assess the character and nature of these occurrences. Therefore, as well as entering the event of 'Cytokine Release Syndrome', with the appropriate grading (see Section 10.4) in the eCRF, please also add the associated AEs (or signs and symptoms), as separate AEs, with the appropriate CTCAE grading as applicable. Fever, hypotension and hypoxia are considered part of CRS, and should be entered in the CRS eCRF page, and therefore do not need to be added as separate AEs.

12.3.4 Adverse Events Associated with CAR T Neurotoxicity (ICANS)

As ICANS can present with multiple signs and symptoms, it is important to assess the character and nature of these occurrences. Therefore, as well as entering the event of 'ICANS', with the

appropriate grading (see Section 10.6) in the eCRF, please also add the associated AEs (or signs and symptoms), as separate AEs, with the appropriate CTCAE grading as applicable (e.g. confusion, aphasia, encephalopathy, seizure).

12.3.5 Serious Adverse Events Reporting

All SAEs occurring during the study must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event. Additional or follow-up SAE reports should be submitted with relevant information promptly. Should the regulatory authority require the Sponsor to submit additional data on the event, the Investigator will be requested to provide additional data to the Sponsor promptly.

Information to be provided for an SAE:

Although most information will have been provided in the eCRF, this information may not always be readily available at the time of evaluating each SAE, or when reporting to the regulatory authorities, so it is essential that as much relevant information is included on the AESI/SAE form. At a minimum, the following is required:

- An identifiable patient (patient ID)
- Reporter details
- The AUTO3 product (if not clear on the AESI/SAE form and if administered)
- The Protocol (if not clear on the AESI/SAE form)
- The AE, with a description of the event and a causality assessment

Please also ensure that this information is accurate, at the time of reporting. Missing information, or information that is inconsistent with the eCRF will automatically generate queries. The initial SAE report will be provided to the Sponsor (or designee) using the AESI/SAE form.

The AESI/SAE form completion and reporting must not be delayed, even if all of the information is not available at the time of the initial report.

The AESI/SAE report should be submitted to the following by fax or email:

- **SAE Fax number:** [redacted]
- **Alternative US Fax number: 1** [redacted]

[redacted]

The 24-hour Safety Hotline: [redacted]

Fax numbers and email address are listed on the AESI/SAE form and in the AESI/SAE form completion guidelines.

SAE follow-up reporting:

After the initial SAE report, the Investigator is required to provide additional follow-up information on the SAE by submitting an updated SAE report form to the Sponsor (or designee). New significant information includes, but is not limited to, the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including resolution.
- Additional narrative information on the clinical course of the event.

Serious adverse events must be followed through to resolution by the Investigator. Resolution is defined as a return to baseline status, Grade 1, or stabilisation of the condition with the expectation that it will remain chronic. For all SAEs, the Investigator may be requested to obtain additional information in an expedited manner. This additional information will allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes such as concomitant medication and illnesses must be provided.

The Medical Monitor may specify a longer period of time, if required to assure the safety of the patient.

12.3.6 Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting

If the event is evaluated as a SUSAR, i.e. unexpected events that are related (reasonable possibility) to the AUTO3, the Sponsor will submit the SUSAR to the regulatory authorities and the Research Ethics Committee, as soon as possible and within 7 calendar days for initial reports of fatal/life threatening events (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events. Where there are conflicting evaluations of causal relationship between the Investigator and the Sponsor, the more conservative will be used for reporting purposes.

All reporting to regulatory authorities will be by the Sponsor, or through a Sponsor designated vendor.

The Sponsor (or designee) will notify Investigators of all SUSARs and reportable SAEs. The Investigator must immediately review with the Investigator site team and retain the documentation in the Investigator Site File.

12.3.7 Adverse Events of Special Interests Reporting

Adverse events of special interest occurring during the study should be reported to the Sponsor within 24 hours of becoming aware of the event using the AESI/SAE form. Additional or follow-up information should be submitted with relevant information promptly.

The AESI/SAE form should be completed and faxed or emailed to the sponsor or designee (see Section 12.3.5) within 24 hours.

12.3.8 Pregnancy Reporting and Management

Pregnancies

Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 12 months after the last dose of study treatment. Any pregnancies during this period must be reported to the Sponsor (or designee) within 24 hours of knowledge of the event using the pregnancy report form (fax numbers and email address are listed on the bottom of the form).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported to the Sponsor immediately using the AESI/SAE Form (i.e. no more than 24 hours after learning of the event).

The Investigator must counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed to immediately inform the Investigator if their partner becomes pregnant during the study or within 12 months after the last dose of study treatment. Any pregnancies during this period must be reported to the Sponsor (or designee) within 24 hours of knowledge of the event using the pregnancy report form (fax numbers and email address are listed on the bottom of the form).

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will be asked to sign an authorisation for use and disclosure of pregnancy health information. The Investigator may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

Outcome

Additional information on the course and outcome of the pregnancy should be provided to the Sponsor (or designee) as soon as becoming available (i.e. no more than 24 hours after obtaining the information) using the paper pregnancy report form. The following pregnancy outcomes will be SAEs and should be reported according to the procedure in Section 12.3.5:

- Spontaneous abortion (as the Sponsor considers spontaneous abortions to be medically significant events).
- Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient.
- All neonatal deaths occurring within 30 days of birth should be reported as SAEs, without regard to causality.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.9 Overdose Reporting and Dosing Errors

Safety information on the study drug may require expedited reporting and/or safety evaluation. This will include:

- Overdose of a study drug (AUTO3 or pembrolizumab)
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a study drug

A study drug overdose is the accidental or intentional use in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. Any overdose or incorrect administration should be noted on the corresponding eCRF page. All AEs associated with an overdose or incorrect administration should be recorded on the AE eCRF page. If the associated AE fulfils the criteria for a SAE, the event should be reported immediately (i.e. no more than 24 hours after learning of the event; see Section 12.3.5).

13 OVERSIGHT COMMITTEES

13.1 SAFETY EVALUATION COMMITTEE

Patient safety will be monitored throughout all parts of the study by a SEC established by the Sponsor. This committee will monitor treatment-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of patients enrolled in this study.

The SEC will be chaired by the Sponsor medical monitor and membership may include Study Investigators, a statistician and biomarker representative, along with additional Sponsor staff as appropriate. The team will meet at regular frequencies throughout study conduct:

During Phase I, the SEC will meet:

1. After the first patient in each cohort completes 2 weeks following AUTO3 infusion.
2. After the third and/or sixth patient in each cohort completes the DLT evaluation period of 28 days to make the dose escalation decision.
3. Additional ad hoc meetings if safety stopping criteria is met.
4. When clinically necessary based on emerging data.

During Phase II, the SEC will meet:

On a periodic basis (not exceeding 3 months until last patient has been enrolled and there after 6 months) to assess cumulative safety data.

2. After 10 and 27 patients (interim analysis) have completed 30 days following AUTO3 infusion.

The Sponsor will maintain documentation of meeting outcomes. Decisions with the potential to impact patient safety (e.g. an unfavourable change in the risk/benefit assessment) will be promptly communicated to Investigators, ethics committees and regulatory authorities as appropriate. Throughout the trial, information regarding all SAEs and potential DLTs will be sent to the SEC members. Dose limiting toxicities will be monitored centrally and the decision to assign the optimal dose will be taken by the SEC.

Dose escalation decisions in Phase I of the study will be made by the SEC. The schedule of dose escalation meetings will depend on the time to completion of a cohort frequency of DLT and when (an) RP2D(s) is/are determined. The SEC may stop further enrolment into one or more of the cohorts if treatment-emergent toxicity is determined to result in an unfavourable change in patient risk/benefit. Decisions and/or recommendations made by the SEC will be communicated to the Principal Investigators at all active study centres and to the Sponsor.

Mandatory SEC processes will be included in a SEC Charter.

13.2 INDEPENDENT DATA MONITORING COMMITTEE

An IDMC consisting of two independent physicians and one statistician will be established by the Sponsor and they will review serious safety events. The decision of the IDMC will supersede that of SEC. The IDMC will meet upon occurrence of the following:

- When any safety stopping, criteria (Section 3.7) are met.
- During Phase I, once during Cohort 1 and once during Cohort 2 (via TC or correspondence).

- Prior to opening Phase II.
- At the interim analysis of Phase II (after enrolling 27 patients in Cohort 1)
- Annually (6-monthly during active enrolment) during Phase II to review cumulative safety data.

Throughout the trial, information regarding all SAEs and DLTs will be sent to the IDMC members to keep them informed on emerging safety findings. IDMC can ask for and will be provided any additional information relevant to the SAEs and DLTs. The IDMC will receive all dose evaluation/escalation meeting minutes (as soon as possible following the meeting) and will have the opportunity to review and can over-rule the SEC decision if clinically warranted and necessary.

When an RP2D(s) decision is made by the SEC, the decision will need to be reviewed and endorsed by the IDMC prior to opening Phase II.

Upon occurrence of any events as defined above, detailed event summaries and cumulative safety data will be sent to the IDMC. A recommendation to continue or to hold or modify the study will be made by the IDMC to the Sponsor. If and when a study is stopped, it will be restarted after a substantial protocol amendment has been approved by the regulatory authorities and ethics committees.

Decisions and/or recommendations made by the IDMC will be communicated by the Sponsor to the Principal Investigators at all active study centres.

Mandatory IDMC processes will be included in the IDMC Charter.

14 STATISTICS

Further details of the statistical analysis of all the endpoints will be included in a separate Statistical Analysis Plan. Any analysis that deviates from the Statistical Analysis Plan will be documented and justified in the Clinical Study Report.

14.1 SAMPLE SIZE ESTIMATION

Approximately 171 patients in total are expected to be enrolled (consented) into Phase I and Phase II of the study and approximately 151 patients in total are anticipated to be treated with AUTO3 therapy.

Phase I (Escalation): Up to 30 patients treated (3 to 6 patients per dose cohort, with the exception of dose level cohort 1 one which may include up to 12 patients [up to 6 patients without anti-PD-1 treatment, and 6 patients with anti-PD-1 treatment]), following a rolling 6 design (Skolnik et al. 2008). An additional 12 patients may be added to RP2D dose /dose range.

Phase I Expansion Cohort: Approximately 20 patients will be treated in an outpatient/ambulatory care setting.

At the end of Phase I (Escalation), assuming there at least 12 patients are treated, the study will terminate if the upper limit of the 2-sided 95% confidence interval in response rate is less than 30%. This is equivalent to observing 0 response in 12 patients. The study will proceed to Phase II if the upper limit of the 2-sided 95% confidence interval in response rate exceeds 30%.

Phase II: In Cohort 1, up to 81 evaluable patients will be analysed using Simon's 2-stage optimal design. This will include 81 patients with DLBCL (and its defined subsets), and those with transformed FL (YESCARTA Prescribing Information 2017, Kymriah US Prescribing Information 2018). Additionally, 20 patients with primary mediastinal large B cell lymphoma and those with lymphoma transformed from other indolent histologies will be enrolled in Cohort 2.

Simon's 2-stage design trial will be used in the Phase II Cohort 1 only. The null hypothesis that the true response rate is 30% will be tested against a 1-sided alternative. In the first stage, 27 evaluable patients will be accrued. If there are nine or fewer responses in these 27 patients, the study will be stopped. Otherwise, 54 additional evaluable patients will be accrued for a total of 81 in Cohort 1. The null hypothesis will be rejected if 31 or more responses are observed in 81 patients. This design yields a type I error rate of 5% and 80% power when the true response rate is 45%.

14.2 DESCRIPTION OF ANALYSIS DATASETS

14.2.1 Screened Set

The Screened Set comprises all patients who have signed informed consent and were screened in the study.

14.2.2 Enrolled Set

The Enrolled Set consists of all patients enrolled into the study.

14.2.3 Infused Set

The Infused Set comprises all patients who received at least one infusion of AUTO3 treatment.

14.2.4 Safety Set

The Safety Set comprises all patients who received at least one dose (complete or partial dose) of AUTO3 therapy.

In addition, safety for patients who received pre-conditioning therapy but not AUTO3 therapy will also be summarized.

14.2.5 Efficacy Analysis Set

All patients in the infused set with PET-positive disease prior to the start of pre-conditioning therapies will be included in the efficacy analysis set (EAS). Patients with PET-negative disease after bridging chemotherapy will not be included in the primary EAS.

Further efficacy analysis sets of patients will be defined in the statistical analysis plan.

14.3 STATISTICAL ANALYSES AND METHODS

Continuous data will be summarised using the mean, median, standard deviation, minimum and maximum, while frequency counts and percentages will be presented for discrete variables. Time-to-event endpoints will be summarised using the Kaplan-Meier method. Summary statistics will be presented for baseline characteristics.

In all analyses, the Study Day refers to the day defined per Clinical Data Interchange Standards (CDISC) convention as:

- (date of the event/assessment − date of first AUTO3 infusion + 1), if the event is on or after the date of first AUTO3 infusion
- (date of the event/assessment − date of first AUTO3 infusion), if the event precedes the date of the first AUTO3 infusion. In this case, the study day will be negative.

Note that the date of AUTO3 infusion will be Day 1 under the CDISC analysis convention.

14.3.1 Primary Endpoints

The primary endpoints of the study are as follows:

Phase I: Safety and RP2D(s)

- Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.
- Frequency of DLT of AUTO3

Phase I: Outpatient Cohort

- Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion.

Phase II: Anti-tumour effect

- Proportion of patients in Cohort 1 treated at RP2D(s) and achieving objective response (CR, PR) per Lugano criteria, post-AUTO3 infusion, based on independent central radiology review.

- Incidence of Grade 3 to 5 toxicity occurring within 75 days of AUTO3 infusion in Cohort 2 at the RP2D(s).

14.3.1.1 Phase I: Safety

Safety associated with AUTO3 administration (only those who received AUTO3).

Summary statistics and analyses will be provided by dose level and overall. The safety analysis set will be used for the analysis of safety data.

Safety evaluations will be based on the incidence, severity and type of AEs, and changes in the patient's vital signs and clinical laboratory results.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) AE coding system for the purpose of summarisation. All AEs occurring in the study will be listed in by-patient data listings. Treatment-emergent AEs will be tabulated, where "treatment-emergent" is defined as any AE that occurs during or after administration of AUTO3 up to 75 days after the last infusion, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline and continues after the first dose of study treatment but worsens in intensity. Events that are considered related to treatment (possibly, probably, or definitely related) will also be tabulated. Adverse events by the NCI CTCAE toxicity grade will also be summarised. Deaths and SAEs will be tabulated in data listings including additional relevant information on the patient.

Laboratory toxicity grades will be calculated for the appropriate laboratory parameters according to NCI CTCAE Version 5.0.

Adverse events of special interest will be analysed in greater depth, including the time to onset and time to resolution where appropriate.

14.3.1.2 Phase I: RP2D(s) and MTD

At the end of the Phase I dose escalation phase, the RP2D(s) will be identified based on the safety data and evaluation of the activity data collected in the dose escalation phase.

14.3.1.3 Phase II: Anti-tumour Effect

The primary endpoints for Phase II **(Cohort 1) will be assessed as follows:**

Proportion of patients in Cohort 1 achieving objective response (CR, PR) per Lugano criteria, post AUTO3 infusion, based on independent central radiology review.

14.3.2 Secondary Endpoints

14.3.2.1 Safety of AUTO3

Reporting of AEs will be based on the latest MedDRA version at the time of database lock and NCI CTCAE Version 5.0. The reporting of CRS and ICANS will be based on the ASTCT consensus grading (Lee et al. 2019). Other AEs that are not defined by the CTCAE should be evaluated for severity per Table 29.

Frequency and severity of treatment-emergent AEs and SAEs will be summarised by time of onset. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple toxicity grades for the same preferred term (PT) will be

summarised under the maximum toxicity grade recorded for the event. Adverse events with missing toxicity grade will be included in the all grades column of the summary tables.

Fatal AEs and SAEs will be listed by patient and summarised by system organ class (SOC) and PT. In addition, AEs occurred prior to AUTO3 infusion will be summarised by SOC and PT in the Enrolled Set.

For laboratory tests covered by the CTCAE, the grades will be derived based on the laboratory values. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. Shift tables using CTCAE grades to compare baseline to the worst post-AUTO3 value will be presented. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges. Shift tables using low/normal/high to compare baseline to the worst post-AUTO3 value will be presented.

Special safety topics including CRS, neurotoxicity, severe hypogammaglobulinaemia etc will be summarised. Details of analyses will be outlined in the statistical analysis plan (SAP).

14.3.2.2 Feasibility of AUTO3 Manufacture in this Patient Population (All Patients)

Feasibility of product generation will be examined by assessing the number of AUTO3 successfully manufactured as a fraction of the number of patients undergoing leukapheresis (all patients registered).

14.3.2.3 Clinical Efficacy of AUTO3

Efficacy will be evaluated in Cohort 1 and Cohort 2 of Phase 2 separately.

Duration of Response: DOR is defined as the time from the first documented disease response (CR or PR) to progression or death due to underlying cancer.

If a patient does not have an event prior to data cut-off, DOR will be censored at the date of the last adequate assessment by default.

Patients who proceed to HSCT after AUTO3 infusion will be censored at the time of HSCT in the main analysis. In addition, a supportive analysis will be performed without censoring HSCT.

Patients who receive new anticancer therapies other than HSCT will be censored at the date of last adequate assessment in the main analysis. In addition, a supportive analysis will be performed without censoring new anticancer therapies.

DOR will be assessed in patients with a BOR of CR or PR in the EAS. Supportive analyses will be performed in the Infused Set and the Enrolled Set. DOR will be summarized by BOR (CR, PR, stable disease/PD) too. The distribution function of DOR will be estimated using the KM method. The median DOR along with 95% CIs will be presented if appropriate.

Progression free survival: PFS is defined as the time from the date of first AUTO3 infusion to the date of first documented progression or death due to any cause.

If a patient does not have an event prior to data cut off, PFS will be censored at the date of the last adequate assessment by default.

Patients who proceed to HSCT after AUTO3 infusion will be censored at the time of HSCT in the main analysis. In addition, a supportive analysis will be performed without censoring HSCT.

Patients who receive new anticancer therapies other than HSCT will be censored at the date of their last adequate assessment in the main analysis. In addition, a supportive analysis will be performed without censoring new anticancer therapies.

PFS will be assessed in all patients in the EAS. Supportive analyses will be performed in the Infused Set and Enrolled Set. The distribution function of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% CIs will be presented if appropriate.

Overall survival will be calculated from the date of AUTO3 infusion to the date of death. Patients who have not died will be censored at the date of last contact (clinic visit or telephone contact). OS will be assessed in all patients in the EAS. Supportive analyses will be performed in the Infused Set and Enrolled Set. The distribution function of OS will be estimated using the KM method. The median OS along with 95% confidence intervals will be presented if appropriate.

Overall Response Rate (ORR) per Lugano criteria and RECIL criteria as assessed by the Investigator will be summarised descriptively with 95% CI.

Incidence of CD19-negative relapse, defined as the proportion of responders who have relapsed and with CD19 being negative at the time of relapse. This will be assessed in all responders in EAS.

14.3.2.4 Expansion and Persistence of AUTO3

Expansion and persistence of CD19/CD22 CAR-positive T cells as determined by PCR will be summarised using the appropriate statistical methods.

- Expansion is defined as the maximum level of CD19/CD22 CAR expression by PCR (copies/µg genomic DNA) assay during follow-up
- Persistence is defined as the duration of detectability, from infusion to the time of last observed detectable concentration.

The kinetics of CD19/CD22 CAR-positive T cells will be documented over time for each patient with AUC calculated, then summarised for all patients descriptively.

Duration of B cell aplasia as determined by flow cytometry in the peripheral blood.

14.3.3 Exploratory

Humoral and cellular immunogenicity against AUTO3 will be evaluated pre- and post AUTO3 treatment.

All analyses for exploratory endpoints outlined in Section 2.3 will be descriptive only. Details will be provided in the SAP.

14.3.4 Interim Analysis

An end of the Phase I analysis will be performed when at least 12 patients have been treated at the RP2D/dose range. Patients treated during the Phase I portion will be pooled for analysis according to the dose received. The overall response rate will be calculated. If the upper limit

of the 95% confidence interval is less than 30% for patients treated at the RP2D(s), the study will be stopped. If the upper limit of the 95% confidence interval is over 30%, the study will continue to the Phase II part of the study.

In Phase II of the study, an interim analysis on response rates will be performed after 27 patients are treated in Cohort 1 and considered evaluable (12 weeks post-treatment of 27th evaluable patient). The study will be stopped in this first stage if fewer than nine responses have been observed. If the response rate has exceeded interim analysis stopping criteria prior to 27 evaluable patients having been treated, then the study will continue to full recruitment without stopping. A formal interim analysis will still be performed based on the first 27 evaluable patients.

15 STUDY COMPLETION, DISCONTINUATION AND WITHDRAWAL OF PATIENTS

15.1 COMPLETION

Patients enrolled will be considered to have completed the study when they have completed assessments until the EOS visit.

15.2 WITHDRAWAL FROM THE STUDY

A patient should be withdrawn before the end of the study if:

- Lost to follow-up
- Withdrawal of consent
- Non-compliance with study procedures
- The Sponsor terminates the study
- Death

The date of withdrawal will be recorded as the EoS visit or the last recorded visit. The reason for discontinuation/withdrawal is to be documented in the eCRF and in the source document.

If a patient is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the patient and to contact the patient's family doctor/general practitioner to obtain information on the patient's status to determine the reason for withdrawal. The measures taken to follow-up must be documented in the source documents and include steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. Any patient who had completed their end of study visit may be invited to re-enrol in the main AUTO3-DB1 study for long-term safety and survival follow-up until the End of Study (36 months after last patient dosed) (Schedule of Assessments Table 4).

For patients who withdraw consent for the study or who are lost to follow-up, the Investigator may consult public records, in order to document survival status in the eCRF.

15.2.1 Procedures for Handling Withdrawals

A patient may voluntarily withdraw their consent at any time during the course of the study without any resulting detriment. All data collected up to the point of withdrawal will be maintained in the study database and included in subsequent analyses, as appropriate. Where a patient is withdrawn from the trial at their own request, or based on a decision of the Investigator, the follow-up should be maintained for safety review, subject to the continuing consent of the patient. The Investigator will discuss the arrangements for withdrawing from any further study interventions and continuing to be followed for safety purposes under the long-term follow-up study.

If a patient is lost to follow-up at a site, every effort should be made to contact the patient's family doctor/general practitioner to obtain information on the patient's status

15.3 REPLACEMENT POLICY

Patients that have disease progression prior to completion of the DLT evaluation period or who are withdrawn from the study for reasons other than toxicity may be replaced, unless the SEC concludes that the patient is evaluable for dose escalation decision making.

16 END OF TRIAL/TERMINATION

The end of the study is defined as 36 months after the last patient has received their first AUTO3 dose or earlier in the event of patient death or consent withdrawal. The study may also be terminated at any time at the discretion of the Sponsor. If the study is terminated due to safety reasons, the Health Authority will be notified per applicable guidelines. Study termination due to business reasons including but not limited to lack of recruitment, will not be considered an early termination requiring immediate notification to the Healthy Authority.

For clinical trials conducted in the EU, a declaration of the end of the clinical trial and early termination, as applicable, will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c) and for those countries outside the EU, local regulations will be followed. In the US, where applicable, the Investigator will notify the IRB in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. A final Clinical Study Report will be provided to the relevant authorities within 12 months after the end of the study.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 ETHICS COMMITTEE REVIEW AND APPROVAL

The final study protocol, including the final version of the written PIS, ICF and any other relevant patient facing material, must be approved, or given a favourable opinion in writing by an IEC/IRB as appropriate.

If it is necessary to amend the protocol or the PIS/ICF during the study, an IEC/IRB approval of the amended protocol and/or PIS/ICF must be obtained prior to implementation of the amended procedures and before new patients are consented to participate in the study using the amended version of the PIS/ICF.

17.2 REGULATORY AUTHORITY REVIEW AND APPROVAL

The study will not commence before approval from the regulatory authority has been granted according to local requirements. The Sponsor (or designee) will be responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of study treatment for shipment to the study site.

During the study, the Sponsor (or designee) is also responsible for submitting subsequent amendments and notifications to the regulatory authority according to local requirements.

17.3 INVESTIGATOR RESPONSIBILITIES

17.3.1 Overall Responsibilities

The Investigator is responsible for conducting the study in full accordance with the clinical study protocol, the latest revision of the Declaration of Helsinki, the GCP: Consolidated Guideline, and all applicable national and local laws and regulations for clinical research. Information regarding any investigational sites participating in this study that cannot comply with these standards will be documented and appropriate actions taken. For studies conducted in the EU/European Economic Area countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the United States or under a United States Investigational New Drug, the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations, subchapter D, part 312, "Responsibilities of Sponsor and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

17.3.2 Site Review

Prior to the study start, the Investigator is required to sign a Protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all the instructions and procedures found in this Protocol, and to give access to all relevant data and records to Clinical Research Associates, auditors and regulatory authorities as required. Investigators ascertain that they will apply due diligence to avoid protocol deviations.

The Investigator will make appropriate reports on the progress of this study to the Sponsor or its designee in accordance with applicable government regulations and their agreement with the Sponsor/Contract Research Organisation.

17.3.3 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from patients prior to conducting any study-related procedures. All consent documentation must be in accordance with applicable regulations and International Council on Harmonisation (ICH) GCP. Each patient is requested to sign and date the ICF after she/he has received and read the PIS and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. Patients will be given adequate time to evaluate the information given to them before signing and dating the ICF. It will also be explained to the patients that they are free to refuse entry into the study or withdraw at any time and without prejudice to future treatment. The ICF must also be signed and dated by the person obtaining consent. The original signed ICF for each patient will be retained on file by the Investigator, a copy will be given to the patient, and a copy will be kept in the patient's hospital notes.

Informed consent forms must be retained for all screened patients and must be available for verification by the Study Monitor at any time.

In the event of changes to the ICF during the study, the Investigator must always use the most current IEC/IRB approved form for documenting written informed consent.

17.3.4 Delegation of Investigator Duties

The Investigator should ensure that all persons involved in the clinical study are adequately qualified, informed about the protocol, any amendment to the protocol, the study treatments, and their study related duties and functions before any involvement takes place. Delegation of any study related duties and documentation of training performed will be recorded in the signature and delegation log.

17.3.5 Communication with IEC/IRB

A list of IEC/IRB members should be obtained by the Investigator or qualified designee and provided to the Sponsor/ representative.

The Sponsor or its designee is responsible for assisting the Investigator with applicable documentation for communication with IECs/IRBs. Before initiating a trial, the Investigator/institution should have written and dated approval of the study protocol, the patient ICF, any written information to the patients, patient recruitment procedures (e.g. advertisement if applicable), the IB, Investigational Medicinal Product labelling (if applicable) and the coordinating Investigator's curriculum vitae to the relevant IEC/IRB for evaluation before the study start. The IEC/IRB's unconditional approval statement will be transmitted by the Investigator to the Sponsor or a designee prior to shipment of AUTO3 to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

During the trial, the Investigator or designee is responsible for forwarding the applicable documents (including protocol deviations, protocol amendments, ICF changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the patients or the conduct of the study; annual updates and/or request for re-approval) for approval and/or review and when the study has been completed. The Investigator or designee will follow national and local requirements.

The Investigator must supply the Sponsor with a copy of the list of members of the IEC/IRB and the letter(s) of approval(s) defining the version of each document approved.

17.3.6 Confidentiality of Trial Documents and Patient Records

The Investigator must ensure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. The Sponsor will maintain confidentiality standards by assigning a unique coded ID number to each patient included in the study. Patient names will never be included in data sets that are transmitted to the Sponsor or their representatives, or to third parties as permitted by the ICF.

On eCRFs or other documents submitted to the Sponsor, patients will not be identified by their names, but by an identification code. The Investigator will keep a patient enrolment log relating codes to the names of patients. The Investigator will maintain documents not for submission to the Sponsor, e.g. patients' written consent forms, in strict confidence. Records will not be destroyed without giving the Sponsor prior written notice and the opportunity to further store such records, at the Sponsor's cost and expense.

After obtaining a patient's consent, the Investigator will permit the study monitor, independent auditor, or regulatory agency personnel to review the portion of the patient's medical record directly related to the study. This shall include all study relevant documentation (e.g. patient medical history to verify eligibility, laboratory test results, admission/discharge summaries for hospital admissions occurring while the patient is enrolled in the study, and autopsy reports for deaths occurring during the study).

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF signed by the patient, unless permitted or required by law.

17.4 LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored by the Sponsor for up to 15 years (or according to local regulations) for additional research. Samples will only be used to further understand AUTO3, to understand advanced cancers, to understand differential drug responders, and to develop tests/assays related to AUTO3 and advanced cancer. The research may begin at any time during the study or the post-study storage period.

Stored clinical samples will be coded throughout the sample storage and analysis process and will not be labelled with personal identifiers. GMP AUTO3-derived samples will be stored according to local GMP rules and procedures.

18 ADMINISTRATIVE REQUIREMENTS

18.1 DATA QUALITY CONTROL AND ASSURANCE

18.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in the approved protocol. All revisions to the protocol must be discussed with and be prepared by the Sponsor. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favourable opinion from the IEC/IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to the study patients.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IEC/IRB approval/favourable opinion. The deviation or change will be submitted as soon as possible to:

- The IEC/IRB for review and approval/favourable opinion.
- The Sponsor.
- Regulatory authority(ies) if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IEC(s)/IRB(s) must be sent to the Sponsor.

If an amendment substantially alters the study design or increases the potential risk to the patient (1) the ICF must be revised and submitted to the IEC(s)/IRB(s) for review and approval/favourable opinion; (2) the revised ICF must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and (3) the new ICF must be used to obtain consent from new patients prior to enrolment.

If the revision is an administrative letter, Investigators must inform their IEC(s)/IRB(s).

18.1.2 Protocol Violations and Deviations

All patients who are enrolled into the study, irrespective of whether or not they receive any treatment, will be followed according to the protocol regardless of the number of treatments received, unless consent for follow-up is withdrawn. Minor protocol deviations that do not result in harm to the study patients or significantly affect the scientific value of the reported results of the study will be recorded. In case of a major protocol deviation occurring (i.e. a deviation that could have a significant effect on the patient's safety, rights, welfare and/or on the integrity of the study data), the Investigator must notify the Sponsor and the appropriate IEC/IRB as soon as possible or as per local requirements. Major protocol deviations that meet the criteria for a serious breach of GCP (e.g. a protocol violation, or non-reporting of critical safety information potentially jeopardising patient safety) should be reported within 24 hours to the Sponsor. The Sponsor is required to report a serious GCP breach within 7 days to the applicable Health Authorities. Protocol deviations will be recorded on the source documents with an explanation for the deviation. No deviation from the inclusion/exclusion criteria will be permitted.

18.1.3 Monitoring

Before the trial can be initiated at a site, the prerequisites for conducting the trial must be clarified and approved by the Sponsor.

Representatives of the Sponsor (or designee) must be allowed to visit all study site locations periodically to assess the data quality and study integrity according to EU directives, ICH GCP, and the FDA regulations. On-site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator and verify that the facilities remain acceptable. With prior agreement from the study site, remote monitoring may also be performed.

Electronic Case Report Form completion and accuracy will be checked by performing source data verification that is a direct comparison of the entries made against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator(s) and/or his/her site staff and resolved. Monitoring procedures require that patients' informed consents, adherence to the inclusion/exclusion criteria and SAE documentation be verified. Additional monitoring activities including requirements for remote monitoring will be outlined in the study specific monitoring plan. The Sponsor may request adequately redacted source documents and hospital records for review by the medical monitor (e.g. pathology reports, imaging reports, cancer treatment history), which may help to better understand the patient's general condition, emerging safety issues, and the activity of AUTO3 efficacy.

The Sponsor must be informed immediately of any change in the personnel involved in the conduct of the trial.

18.1.4 Audits and Site Inspections

Authorised personnel from domestic and foreign regulatory authorities and the Sponsor Quality Assurance (or designee) may carry out inspections and audits respectively. The purpose of an audit/inspection is to ensure that ethical, regulatory and quality requirements are fulfilled in the Sponsor studies.

The Investigator will permit international, national, and local Health Authorities, the Sponsor monitors, representatives, and collaborators, and the IECs/IRBs to inspect facilities and records relevant to this study. The Investigator should promptly notify the Sponsor or their authorised representative of any inspections scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or their authorised representative.

18.2 DATA HANDLING AND RECORD KEEPING

18.2.1 Data Management

Data for each patient will be entered into the (Sponsor-approved) clinical database via electronic data capture [EDC]) in a timely manner. The EDC application uses system controls to ensure that unauthorised users cannot access or modify data. All users must have successfully undergone EDC application training prior to entering data into the EDC system. Electronic Cases Report Forms should be reviewed and electronically signed and dated by the Investigator or a designee. The eCRF system will be compliant with FDA Code of Federal Regulations 21 Part 11 and EU Clinical Trial Directive (EC) No. 2001/20/EC.

It is the responsibility of the Investigator to ensure that the data included in the eCRF is accurate, complete, and electronically signed where appropriate.

The data will be electronically verified through use of on-line checks during data entry and through programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the investigational site personnel. Data entered into the eCRF will be validated as defined in the data validation specifications. All updates to queried data will be made by authorised study site personnel only, and all modifications to the database will be recorded in an audit trail. Once all the queries have been resolved, eCRFs will be locked by password protection. Any changes to locked eCRFs will be approved by the Investigator. Once the full set of eCRFs have been completed and locked, the Sponsor will authorise a database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then only be made with written agreement of the Sponsor.

Adverse events and medical/cancer history terms will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities. Prior and concomitant medications and therapies will be coded according to the World Health Organisation drug dictionary. Coding review will be performed by the Sponsor (or designee) prior to database lock.

At the end of the study, the clinical data will be transferred to the Sponsor and the investigative site will receive patient data for their site in a readable format that must be kept with the study records.

18.2.2 Study Documentation and Retention of Records

The Investigator must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation should include but is not limited to, protocols, eCRF data, SAE reports, patient source data, correspondence with Health Authorities and IEC/IRBs, ICFs, Investigator(s) and study team members' curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory directors' curricula vitae (essential documentation listed in ICH GCP [CPMP/ICH/135/95]). Patient files and other source data must be kept for the maximum period of time required by applicable regulations and guidelines or institution procedures or for the period specified by the Sponsor, whichever is longer. The Sponsor must be consulted if the Investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for the specified period.

The patient medical records must contain the product name/code, the trial reference code, trial patient code and administration dates and dose in order to ensure that a link can be made back to the identity of the product and further traceability records of the Investigator and Sponsor.

18.3 CLINICAL TRIAL AGREEMENT, FINANCE, AND INSURANCE

This study will be conducted under a Clinical Trial Agreement between Autolus Limited ("Sponsor") and the institution(s) representing the investigational study site(s) ("Investigator"). Financial support to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of the Investigator and the Sponsor, and will form the contractual basis under which the clinical study will be conducted.

A Certificate of Clinical Trials Insurance will be provided to the study centres by the Sponsor, where required. Details of the Sponsor's arrangement for clinical study insurance to provide for compensation to patients for any claim for bodily injury or death arising from participation in the clinical study are provided in the PIS.

19 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Both the EU Data Protection Regulations and the FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical trials of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors requires study registration as a condition for publication of research results generated by a clinical study (http://www.icmje.org).

All information supplied by the Sponsor in connection with this study and not previously published to the public, is considered confidential information ("Confidential Information"). This confidential information includes, but is not limited to, the IB, clinical protocol, eCRFs and other scientific data. Any data collected during the study are also considered confidential information. This confidential information shall remain the sole and exclusive property of the Sponsor, shall not be disclosed to others without prior written consent of the Sponsor, and shall not be used except in the performance of this study.

The information developed during the conduct of this study is also considered confidential information, and will be used by the Sponsor in connection with the development of the ATIMP. The confidential information may be disclosed as deemed necessary by the Sponsor. To allow the use of the confidential information derived from this study, the Investigator is obliged to provide the Sponsor with complete test results and all data developed in this study.

The Sponsor has full ownership of the original eCRFs completed as part of the study.

By signing the Clinical Study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

Should the Investigator wish to publish the results of this study, the Investigator agrees to provide the Sponsor with a manuscript for review 60 days prior to submission for publication.

The Sponsor retains the right to delete from the manuscript, information that is confidential or proprietary and to object suggested publication and/or its timing (at the Sponsor's discretion).

In addition, if requested by the Sponsor, the Investigator shall withhold publication an additional 6 months to allow for filing a patent application or taking such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

In the event that the Sponsor chooses to publish the data from this study, a copy will be provided to the Investigator at least 30 days prior to the expected date of submission to the intended publisher (Fitzgerald et al. 2016).

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21 APPENDICES

Appendix 1: Patient with NHL will be Evaluated using Response Criteria for Non-Hodgkin Lymphoma for Documenting Disease Response

Lugano Classification (Cheson et al. 2014)

Response	Site	PET-CT-Based Response	CT-Based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g. with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in the longest transverse diameter of the lesion (LDi). No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Response	Site	PET-CT-Based Response	CT-Based Response
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extra-lymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in sum of the product of the perpendicular diameters for multiple lesions (SPD) of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None
	Bone Marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Response	Site	PET-CT-Based Response	CT-Based Response
No response or stable disease		**No metabolic response**	**Stable disease**
	Lymph nodes and extralymphatic sites	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease		**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following:**
	Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	Cross product of the LDi and perpendicular diameter (PPD) progression (as defined below for extranodal lesions).
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm, and increase by ≥50% from PPD nadir, and an increase in LDi or SDi from nadir: 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g. a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions

Response	Site	PET-CT-Based Response	CT-Based Response
	New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (e.g. infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS=5-point scale; CT=computed tomography; FDG=fluorodeoxyglucose; IHC=immunohistochemistry; LDi=longest transverse diameter of a lesion; MRI=magnetic resonance imaging; PET=positron emission tomography; PPD=cross product of the LDi and perpendicular diameter; SDi=shortest axis perpendicular to the LDi; SPD=sum of the product of the perpendicular diameters for multiple lesions.

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under-treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g. liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability, but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g. GI tract, liver, bone marrow), fluorodeoxyglucose uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g. with marrow activation as a result of chemotherapy or myeloid growth factors).

b PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

Appendix 2: Eastern Cooperative Oncology Group Performance Status Score

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken et al. 1982).

Appendix 3: Highly Effective Methods of Birth Control

For females of childbearing potential (defined as <24 months after last menstruation or not surgically sterile), a negative serum or urine pregnancy test must be documented at screening, prior to conditioning and confirmed before receiving the first dose of study treatment (AUTO3). Pregnancy testing will also occur during the follow-up period (Day 28, Day 56, Month 3, Month 6, Month 12, Month 18 and Month 24), as outlined in the Schedule of Assessments. (Note: If patient discontinues study due to disease progression pregnancy testing will stop at Month 12).

For females who are not postmenopausal (<24 months of amenorrhea) or who are not surgically sterile (absence of ovaries and/or uterus), two methods of contraception comprising of one highly effective method of contraception together with a barrier method must be used during the treatment period and for at least 12 months after the last dose of study treatment. They must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 12 months after receiving the last dose of study drug.

For males, it must be agreed that two acceptable methods of contraception are used (one by the patient – usually a barrier method, and one highly effective method by the patient's partner as defined below) during the treatment period and for at least 12 months after the last dose of study treatment and that sperm will not be donated during the treatment period and for at least 12 months after the last dose of study treatment.

Highly effective methods of birth control:

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device [2]
- Intrauterine hormone-releasing system [2]
- Bilateral tubal occlusion [2]
- Vasectomised partner [2, 3]
- Sexual abstinence [4]

[1] Hormonal contraception may be susceptible to interaction with the AUTO3, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that the vasectomised partner is the sole sexual partner of the women of child bearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Birth control methods that may NOT be considered as highly effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide [5]
- Cap, diaphragm or sponge with spermicide [5]

[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but NOT highly effective, birth control methods.

Birth control methods that are considered UNACCEPTABLE in clinical trials

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhoea method are not acceptable methods of contraception.
- Female condom and male condom should not be used together.

Birth control methods that are considered ACCEPTABLE in clinical trials

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.
- Female sterilisation (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilisation (at least 6 months prior to screening). For female patients on the study the vasectomised male partner should be the sole partner for that patient.
- BOTH of the following forms of contraception must be utilised:
    a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

- Use of IUDs are excluded due to increased risks of infection and bleeding in this population.
- In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment.

Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months or have undergone hysterectomy, salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Acceptable documentation includes written or oral documentation communicated by clinician or clinician's staff of one of the following:

- Demographics show age <11.
- Physical examination indicates Tanner Stage 1.
- Physician report/letter.
- Operative report or other source documentation in the patient record.
- Discharge summary.
- Follicle stimulating hormone measurement elevated into the menopausal range.

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